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A THIRD YEAR COURSE OF ORGANIC CHEMISTRY

THE HETEROCYCLIC COMPOUNDS, CARBOHYDRATES, AND TERPENES

BY

T. P. HILDITCH

D.Sc.(Lond.), F.I.C.

WITH NUMEROUS DIAGRAMS

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First Published in 1914

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TO

MY TEACHER

PROFESSOR J. NORMAN COLLIE, F.R.S.

PREFACE

THIS volume is intended to form the sequel to Dr A. E. Dunstan's "First Year Organic Chemistry," and to Mr F. B. Thole's "Second Year Organic Chemistry" Dr Dunstan's work deals with the aliphatic group of organic compounds, and is necessarily to some extent elementary, whilst the Second Year course embraces the carbocyclic or benzene group. The present book completes the series by a survey of the heterocyclic compounds, followed by a study of certain groups of aliphatic and carbocyclic substances, which, by reason of their complexity, are omitted from detailed consideration by students in the earlier periods of their course. These include, on the aliphatic side, the sugars and the polypeptides, and, on the other hand, the terpenes or hydroaromatic compounds.

I have made free use of the standard authorities on the various subjects enumerated, notably Richter's "Organische Chemie," Wedekind's handbook on the heterocyclic series, and Lippmann's "Chemie der Zuckerarten"; whilst my efforts to bring the volume as far as possible up to date have been assisted especially by the Chemical Society's "Annual Reports," by Dr A. W. Stewart's "Recent Advances in Organic Chemistry," and by the lectures delivered on Advanced Organic Chemistry at University College, London, by Assistant Professor Smiles, D.Sc.

Much kind assistance in the arrangement of the numerous block-formulæ has been afforded by Messrs F. Fox and H. Christopher, B.Sc., and in proof-reading and indexing by the latter, Dr A. E. Dunstan, and my wife, to all of whom I offer my grateful thanks.

T. P. H.

GRAPPENHALL

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THIRD YEAR ORGANIC CHEMISTRY

CHAPTER I

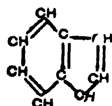
HETEROCYCLIC COMPOUNDS

(INTRODUCTORY TO CHAPTERS II-X)

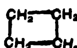
WHEN one commences the study of organic chemistry or, to give that science its alternative name, the chemistry of carbon compounds, one learns, in the first place, of the peculiar capacity possessed by the atoms of carbon for linking up together in long chains, so that we may have as many as sixty carbon atoms united to each other in this manner. Although the vast majority of organic compounds are not so complex as this, it is frequent to find any number of carbon atoms from two to twelve serving as a nucleus for the attachment of other elements such as oxygen, hydrogen, or nitrogen, and thus we may gather from a survey of these *aliphatic* compounds (in which the carbon atoms are arranged in long, simple, or branched chains, without any ring formations) that the characteristic chemical property of carbon is its habit of uniting with itself or with other non-metallic elements to form compounds of all possible degrees of complexity (or simplicity). This behaviour is no doubt connected in some way with the position of carbon in the periodic system of the elements, where it falls in the centre of the first period (elements of least atomic weight), and possesses, according to Abegg's views, an equal number of "normal" (positive) and "contra" (negative) valencies—four in each case.

The chief types of carbon compounds (hydrocarbons, alcohols, ethers, ketones, acids, etc.) having been thus encountered in the aliphatic series, one usually proceeds to consider the nature of benzene and its many derivatives, and finds that a new system

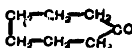
of carbon-atom combination must be assumed in these series, namely, the presence of a *closed chain* or ring-system of six carbon atoms. In much smaller number one meets with rings of five, four, seven, or eight carbon atoms (as, for example, in the respective cases of indene (I), tetramethylene (II), suberone (III), or cyclooctane (IV)).



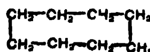
I



II

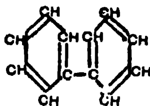


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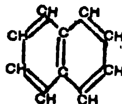


IV

One finds also that two or more of these ring-systems may be joined together in a very intimate way; taking the case of two phenyl groups, these may be united as in diphenyl (V), which is simply a benzenoid hydrocarbon, or, again, they may be so "condensed" together as to form naphthalene (VI), the parent substance of an entirely fresh series of compounds.

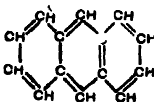


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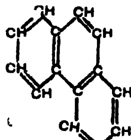


VI

Ring-systems such as that of naphthalene are said to be made up of "condensed," "conjugated," or (better) "*annealed*" benzene nuclei; it is also evident that when more than two benzene nuclei are thus combined, there is a possibility of two kinds of *annealation—linear*, as in anthracene (VII) and *angular*, as in phenanthrene (VIII).



VII



VIII

We see, therefore, that besides the simple open-chain or

aliphatic compounds there are many others derived from closed carbon chains—*carbocyclic* or *homocyclic* compounds.

Now the aliphatic substances may be sub-divided as follows:—

(*a*) *Compounds containing an unbroken chain of carbon atoms.* We may take normal pentane, $CH_3.CH_2.CH_2.CH_2.CH_3$, as a case in point; this is said to be a *homocatenic* compound.

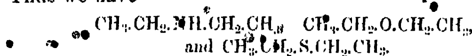
(*b*) *Compounds containing a chain of carbon atoms with other non-metallic elements also in the chain.* Any of the methylene groups ($-CH_2-$) in pentane may be replaced by either of the following:


- NH -,

O ,

or

Thus we have


$CH_3.CH_2.NH.CH_2.CH_3$, $CH_3.CH_2.O.CH_2.CH_3$, and $CH_3.CH_2.S.CH_2.CH_3$.

Such compounds are distinguished as *heterocatenic*.

It is found, however, that a similar state of affairs persists in the homocyclic, as well as the aliphatic, series. Here we meet with the following substitutions:—

	Homocyclic.	Heterocyclic.		
(*a*)	$-CH_2-$	$-O-$	$-S-$	$-NH-$
(*b*)	$-CH=$	$-O=$	$-S=$	$-N=$

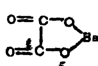
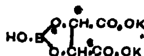
In series (*b*), corresponding to the actual benzenoid derivatives, there are formed, on replacement as above, compounds containing quadrivalent oxygen or sulphur, and tervalent nitrogen, all of which groups are strongly basic in character. It is natural, therefore, that in such cases the chemical character of the benzenoid radicle should be entirely altered.

At the same time, the *heterocyclic* complex so obtained has in a great many cases quite as strong an individuality as that of benzene, and the heterocyclic ring-system, together with its main chemical characteristics, persist unchanged through a whole series of derivatives of the parent substance. Moreover, many of these heterocyclic derivatives are of great interest, since a large number occur naturally as vegetable or animal products,

others are valuable artificial colouring matters, and some, again, are equally important synthetic medicines.

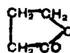
It is consequently appropriate to make a separate study of this branch of organic chemistry, and to this end the first part of the present treatise is devoted.

At the outset, however, we must define somewhat carefully the limits of the subject. From a general standpoint, substances such as barium oxalate or potassium boro-tartrate have every right to be regarded as heterocyclic compounds:

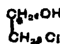
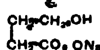



Compounds of this kind, which, being salts, are at once resolved into open-chain compounds by mild reactions of double decomposition, are not of the well-defined heterocyclic nature which characterizes those already mentioned.

Again, other substances, such as ethylene oxide or γ-butyrolactone,

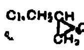



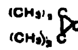
are intermediate, in stability to hydrating agents, between salts such as barium oxalate and a well-defined heterocyclic compound such as furfurane (p. 45). On the one hand, they may be resolved by suitable reagents into open-chain derivatives, *e.g.*,

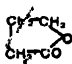



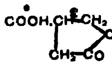
whilst at the same time well-defined homologous series of each type exist. Thus we have:

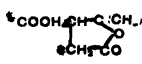

Ethylene oxide.


Epichlorhydrin.


Tetramethylethylene oxide.


γ-Butyrolactone.


Paraconic acid.


Terebic acid.

Hence no strict definition of a heterocyclic compound can be formed to include substances in which a definite heterocyclic nucleus persists unchanged throughout a given series, and at the same time to exclude unstable heterocyclic nuclei; for there is no well defined boundary between the two classes.

For the purposes of this book, however, we may proceed as follows: (i) We shall only consider the heterocyclic compounds derived from substitution of *carbon* by *oxygen*, *sulphur*, or *nitrogen*. (ii) We shall confine our attention to the better-defined heterocyclic rings containing *three*, *four*, *five*, or *six* atoms in the nucleus.

A definition of the following nature may therefore be arrived at:

A heterocyclic compound (parent substance) *is one which gives rise to a well-defined series of homologous or substituted derivatives, maintains its distinctive nature throughout such series, and is derived from the corresponding homocyclic compound* (containing *n* carbon atoms in the ring-system) *by substitution of not more than* n – 1 *carbon atoms by* n – 1 *atoms of oxygen, sulphur, or nitrogen.*

It is significant that nitrogen is by far the most frequent ring-component in heterocyclic systems, sulphur and oxygen following; for in the realm of inorganic compounds, nitrogen is equally remarkable for its tendency to ring formation, as in hydrazoic acid and other derivatives, whilst again, sulphur and oxygen each exist in polymolecular forms (S_8, O_3), very probably possessing a cyclic structure. The parallelism between inorganic cyclic compounds and the heterocyclic compounds of these three elements is indeed of a quantitative rather than a qualitative or superficial order.

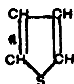
The chief types of heterocyclic compounds must now be classified in accordance with the above definition. The most convenient system of classification is to consider separately the *three-*, *four-*, *five-*, and *six*-membered rings, and to subdivide these according to the number and nature of the heterogeneous atoms. Where the latter are of more than one kind, we must define a method of reference such as the following:—

If a substance contains oxygen and sulphur as ring components, it will be

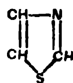
considered as a *sulphur ring-substituent* of the corresponding *oxygen ring-system*, e.g.,



whilst substances containing sulphur (or oxygen) and nitrogen as ring-components will be considered as *nitrogen ring-substituents* of the corresponding sulphur (or *oxygen*) complex :

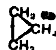


and



THREE-MEMBERED RING SYSTEMS. (III)

Nearest carbocyclic analogue : *Cyclopropane*,



Hetero-Atoms : *Oxygen* (O). *Sulphur* (S). *Nitrogen* (N).

1.

Ethylene oxide, p. 19. Tolane sulphide, p. 22. Ethyleneimide, p. 21.

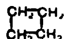
2. — —



Diazomethane, p. 22.

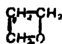
FOUR-MEMBERED RING SYSTEMS. (IV)

Nearest carbocyclic analogues : *Cyclobutane*,



Hetero-Atoms : *Oxygen* (O). *Sulphur* (S). *Nitrogen* (N).

1 (*a*)

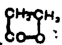


—

CH₂—CH₂ / CH₂—NH

Trimethylene oxide, p. 19. Trimethylene imide, p. 21.

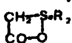
1 (*b*)



— —

β-Lactones, p. 30.

2 (*a*)



—

Thetines, p. 31.

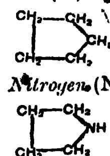
(*b*)

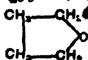
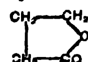
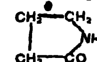
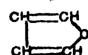
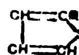
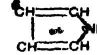
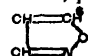
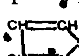
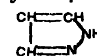
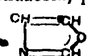
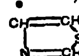
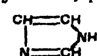
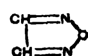
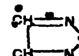
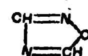
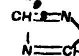
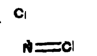
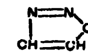
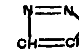
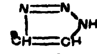
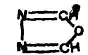
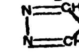
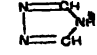
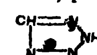


Betaines, p. 36.

FIVE-MEMBERED RING SYSTEMS (V)

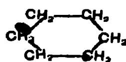
Nearest carbocylic analogue: *Cyclopentane*,



Hetero-Atoms:	*Oxygen* (O).	*Sulphur* (S).	*Nitrogen* (N).
1 (*a*)	 Tetramethylene oxide, p. 20.	—	Pyrrolidine, p. 53.
(*b*)	 γ-Lactones, p. 25.	—	 γ-Lactams, pp. 29, 54.
1 (*c*)	 Furfurane, p. 45.	 Thiophene, p. 49.	 Pyrrol, p. 5[illegible].
2 (*a*)	 Isoxazoles, p. 64.	 Isothiazoles, p. 65.	 Pyrazoles, p. 64.
(*b*)	 Oxazoles, p. 71.	 Thiazoles, p. 71.	 Glyoxalines, p. 72.
(*c*)	—	—	 Cyclic ureides, p. 194.
3 (*a*)	 Azoxazoles, p. 75.	 Thio(aa')diazoles, p. 76.	 Osotriazoles, p. 77.
3 (*b*)	 Azoximes, p. 76.	 Azosulphimes, p. 76.	 Triazoles, p. 78.
3 (*c*)	 Diazooxides, p. 76.	 Diazosulphides, p. 76.	 Azimides, p. 79.
3 (*d*)	 Oxybiazoles, p. 77.	 Thiodiazoles, p. 77.	 Triazoles, p. 78.
4	—	—	 Tetrazoles, p. 79.

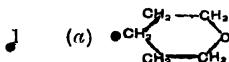
SIX-MEMBERED RING SYSTEMS. (VI)

Nearest carbocyclic analogues:

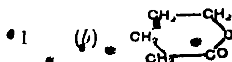
Cyclohexane 

and *Benzene* 

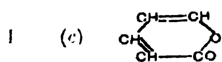
Hetero-Atoms: *Oxygen* (O). *Sulphur* (S). *Nitrogen* (N).

1 (*a*) 

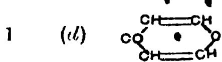
Pentamethylene oxide, p. 19. — Piperidine, p. 121.

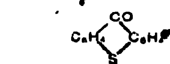
1 (*b*) 

δ-Lactones, p. 27. — δ-Lactams, p. 29.

1 (*c*) 

α-Pyrones, p. 82. — α-Pyridones, p. 107

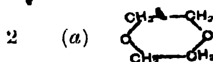
1 (*d*) 



γ-Pyrones, p. 81. (Thioxanthones, p. 96.) γ-Pyridones, p. 1

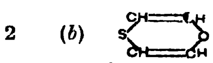
1 (*e*) — — 

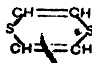
Pyridine, p. 102.

2 (*a*) 

— —

Diethylene dioxide, p. 167.

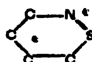
2 (*b*) 

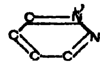


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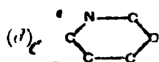
(Phenoxthines, p. 168.) (Thianthrenes, p. 168.)

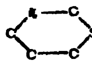
(*c*) 

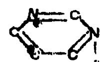




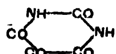
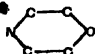
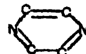
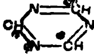
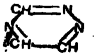
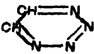
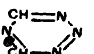
o-Oxazines, p. 176. *o*-Thiazines, p. 176. *o*-Diazines, p. 170.

(*d*) 



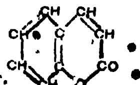


m-Oxazines, p. 176. *m*-Thiazines, p. 176. *m*-Diazines, p. 17

Hetero-Atoms :		Oxygen (O).	Sulphur (S).	Nitrogen (N).
2	(e)	—	—	 Cyclic ureides, p. 194.
2	(f)	 *p*-Oxazines, p. 177.	 *p*-Thiazines, p. 178.	 *p*-Diazines, p. 172.
3	(a)	—		 β-Triazines, p. 187.
3	(b)	—		 Cyanidines, p. 185.
3	(c)	—		 α-Triazines, p. 187.
4	(a)	—	—	 Osotetrazines, p. 188.
4	(b)	—	—	 Tetrazines, p. 188.

Most of these numerous types are also found annealed with one or more benzenoid residues, and indeed in many cases the *benzo-derivatives*, as they are called, are more stable than the simple heterocyclic compounds. Examples of annealed benzene-heterocyclic nuclei are:

Benzo-α-pyrone.



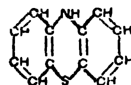
Coumarin.

Benzopyrrol.



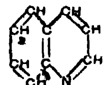
Indol.

Dibenzo-*p*-thiazine.



Thiodiphenylamine.

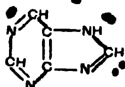
Benzopyridine.



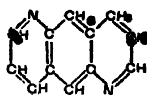
Quinoline.

Less frequently the fusion of two heterocyclic ring systems is to be noticed, as in the following cases :

m-Diazine and Glyoxaline. Pyridine and Quinoline.



Purine.



Phenanthroline.

For purposes of reference, it may be well to recast the system of heterocyclic nuclei given above in the order in which it will be treated in succeeding chapters :

Page.	Chapter.	Ring-systems.	Types of Heterocyclic Compound.
18	II	3- and 4-membered.	Alkylene oxides (III, O, 1 ; IV, O, 1a ; V, O, 1a ; VI, O, 1a), sulphides (III, S, 1), imides (III, N, 1 ; IV, N, 1a) ; aliphatic diazocompounds (III, N, 2).
25	III	4-, 5-, 6-membered.	β-, γ-, and δ-Lactones (IV, O, 1b ; V, O, 1b ; VI, O, 1b), thetines (IV, S, 2a), and betaïnes (IV, N, 2b).
41	IV	5-membered.	Furfurane (V, O, 1c), thiophene (V, S, 1c), pyrrol (V, N, 1c), pyrrolidine (V, N, 1a), and their mono- and di-benzo-analogues.
62	V	5-membered.	The azoles : (*a*) Isoxazoles (V, O, 2a), Isothiazoles (V, S, 2a), pyrazoles (V, N, 2a) ; (*b*) Oxazoles (V, O, 2b), thiazoles (V, S, 2b), glyoxalines (V, N, 2b) ; (*c*) Azoxazoles (V, O, 3a), azoximes (V, O, 3b), diazo-oxides (V, O, 3c), oxy-diazolines (V, O, 3d), thio(aa_1)diazoles (V, S, 3a), azosulphimes (V, S, 3b), diazosulphides (V, S, 3c), thiodiazolines (V, S, 3d) ; (*d*) Osotriazoles (V, N, 3a), azimides (V, N, 3c), and triazoles (V, N, 3b and 3d) ; (*e*) Tetrazoles (V, N, 4).
81	VI	6-membered.	α- and γ-Pyrones (VI, O, 1c and 1d), chromones and xanthones (mono- and di-benzo-γ-pyrones), thioxanthones (VI, S, 1d).
98	VII	6-membered.	Pyridine (VI, N, 1c), piperidine (VI, N, 1a), and their mono- and di-benzo-analogues.

Page.	Chapter.	Ring-systems.	Types of Heterocyclic Compound.
131	VIII	—	The alkaloids (mainly derived from *pyridine*, *quinoline*, and iso-*quinoline*).
166	IX.	6-membered.	Diethylene dioxide (VI, O, 2a), phenoxthines (VI, O, 2b), thianthrenes (VI, S, 2b), pyridazines (VI, N, 2c), pyrimidines (VI, N, 2d), pyrazines, quinoxalines, phenazines (VI, N, 2f), oxazines (VI, O, 2c, 2d, 2f), thiazines (VI, S, 2c, 2d, 2f), triazines (VI, N, 3a, 3b, 3c), and tetrazines (VI, N, 4a, 4b).
189	X	9-membered.	The purines (derived from an annealed *pyrimidine glyoxaline* nucleus) (VI, N, 2d and V, N, 2b); and cyclic ureïdes (V, N, 2c; VI, N, 2e).

Characteristics and Relative Stability of Different Heterocyclic Ring-systems.—In spite of the variety and bewildering abundance of the heterocyclic systems revealed in the above tables, it is possible at once to point out a number of characteristics which are common to the whole group.

Taking first of all the number of atoms composing the different ring-systems, it is evident that the five- and six-membered rings are by far the most common. Hence it appears that the atoms, other than carbon, present in the ring complex are closely related, so far as their atomic size and spacial arrangement is concerned, to a carbocyclic carbon atom; or, at all events, the heterogeneous atoms would seem to have accommodated themselves in some way to the habits of their carbon neighbours, since, as is well known, the most stable carbocyclic systems comprise rings of five or six carbon atoms. Accordingly, if we assume Baeyer's Strain Theory as an explanation of the relative stability or instability of carbocyclic rings, clearly the same hypothesis applies to the heterocyclic series, so that, even if an absolute tetrahedral arrangement of the oxygen, sulphur, or nitrogen atoms in these substances is not assumed, it must be supposed that the direction of their valencies (operative in forming the cyclic chain) is much the same as that of similarly combined carbon.

Again, the three- and four-membered ring compounds, like

their carbocyclic analogues, are exceedingly readily rearranged into open-chain derivatives.

Another most important influence is the *nature* of the heterocyclic ring substituents. In any given series, for example, *furfurane, thiophene*, and *pyrrol*, the nature of the heterocyclic substance is seen to be influenced to some extent by the electrochemical nature of the hetero-atom.

Thus furfurane and thiophene, containing respectively the relatively inert bivalent oxygen and sulphur, are neither acidic nor basic in character, whilst pyrrol is a well-defined base, in virtue of the tervalent nitrogen present.

At the same time, a marked reflex influence of the carbocyclic part of the nuclus upon the hetero-atoms is noticeable.

The oxygen in furfurane is not in the least ethereal in nature; the sulphur in thiophene differs from that in an alkyl sulphide, both in physical characteristics, such as atomic refractivity, and also in chemical behaviour, for it is perfectly indifferent to oxidizing agents which would convert the latter compound to a sulphone; finally, the nitrogen in pyrrol is acidic, as well as basic, and the imino-hydrogen can be directly replaced by certain metals.

This behaviour is reminiscent of that of an imino-group situated between two unsaturated groups (for example – CO – NH – CO –); and indeed the factor which is causing the anomalous behaviour of the hetero-atoms is clearly the *residual affinity* of the unsaturated carbocyclic nucleus, for if this is hydrogenized, the resulting products are entirely analogous in chemical behaviour to alkyl compounds of similar type.

As instances of this, it may be stated that tetrahydrofurfurane (tetramethylene oxide) reacts as an ordinary alipathic ether, and that tetrahydropyrrol (pyrrolidine) is indistinguishable in its general behaviour from any other dialkylamine, being an exceedingly strong organic base.

Returning, however, to the specific influences of nitrogen, sulphur, and oxygen as hetero-atoms, it was stated (page 5) that the parallelism between the inorganic and the organic cyclic derivatives of these elements was more than superficial.

Nitrogen is marked in its inorganic compounds by its ability to form ring complexes possessing well-defined properties: nitrogen is found as a ring component of by far the greater number of the more stable and well-characterized heterocyclic systems. Moreover, just as the basic nature of ammonia and hydrazine gives place to the acidic explosive compounds of the azoimide and related types, so the basic nature and great stability of the mono-nitrogenous heterocyclic substances (pyridine, pyrrol, pyrazole, etc.) gradually falls off as more unsaturated nitrogen atoms are accumulated in the ring, until compounds such as the triazoles, tetrazoles, and tetrazines (containing residues of the type $-N=N-N=N-$) are found to be unstable, explosive, and usually acidic.

Sulphur, again, shows a tendency in inorganic compounds to form complex molecular derivatives, such as the polysulphides of the metals, the polythionic acids, or the polymeric forms of the element itself, although in many cases the products are not so well defined as the inorganic nitrogen complexes. A similar behaviour is seen in many heterocyclic compounds of sulphur; these are frequently of a very stable nature, but are usually much less reactive than the analogous nitrogen derivatives. Frequently, too, heterocyclic sulphur complexes of quite abnormal types have been met with; these are apparently in many cases produced by a kind of polymerization of a simpler ring containing sulphur.

Finally, oxygen forms less stable and less definite heterocyclic series than either sulphur or nitrogen.

If, however, the oxygen or sulphur atom, instead of being bivalent, is quadrivalent (and therefore of an order of basicity approaching that of nitrogen), the case is entirely altered, and heterocyclic compounds containing quadrivalent atoms of these elements are as well defined as any of the nitrogen series. We may quote the pyrones (quadrivalent oxygen) and many of the "suphur dyestuffs" in support of this statement.

There are thus at least *three main characteristics* of any heterocyclic nucleus, namely,

(i) *The total number of atoms in the ring.*

(ii) *The specific nature of the heterocyclic atoms.*

(iii) *The specific effect of the purely carbocyclic portion of the heterocyclic residue.*

To these a *fourth influence*, of an external nature, must be added—*the effect of external substituents on ring stability.*

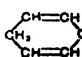
It may be stated that, as a rough general rule, electro-negative or acidic substituents tend to ring stability, and conversely.

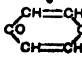
A few examples of this may be given.

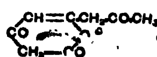
(*a*) *Ethylene oxide*, $\begin{array}{l}CH_2\\ \,|\!>O\\ CH_2\end{array}$ is not a very well-marked heterocyclic compound, since its ring system may be ruptured by the action of warm aqueous potash. On the other hand, *ethylene chlorohydrin* is much more stable, whilst *tetramethylethylene oxide*, containing the more electro-positive *methyl* in place of hydrogen, is so unstable that it unites at once with cold water, the ring-system being split up.

(*b*) Similarly, *diazoacetic ester*, $\begin{array}{l}N\\ \|\!>CH\cdot COOEt\\ N\end{array}$, is more stable than *diazomethane*, $\begin{array}{l}N\\ \|\!>CH_2\\ N\end{array}$

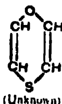
(*c*) The influence of substituents on the stability of five- and six-membered rings is naturally not so prominent, but it is well to recall that certain members of these classes exist only in the form of their hydroxyl or carboxyl derivatives. Thus the parent substance (I) of γ-pyrone (II) and dehydracetic acid (III) is unknown;

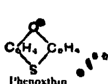

I

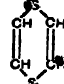

II

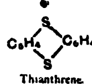

III

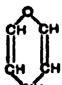
(*d*) Quite a number of other six-membered ring-systems (chiefly of the (less stable) oxygen and sulphur series) are only known in the form of their *dibenzo*-derivatives, the two acidic phenylene residues apparently promoting stability; for example:

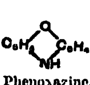

(Unknown)

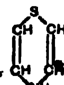

Phenoxthin

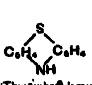

(Unknown).


Thianthrene.


(Unknown)


Phenoxazine.


(Unknown).


Thiodiphenylamine

Synthetic Formation of Heterocyclic from Open-chain Compounds.—It is obviously impossible to give general methods of preparation for so vast a range of series as those which have been outlined in the preceding tables; but it will be well to indicate at this point a very few of the means which, whilst embodying similar

principles may be applied to the production of widely different compounds.

I. *Pyrogenetic Reactions.* — Certain heterocyclic compounds result when vapours of non-heterocyclic bodies are heated to redness (in a similar manner to the production of benzene from acetylene):—

(*a*) *Pyridine* is thus produced from acetylene and prussic acid:

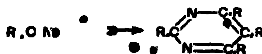


$$2C_2H_2 + HCN \rightarrow C_5H_5N.$$

(*b*) *Carbazole* results from diphenylamine at a red heat:



(*c*) *Pyrimidines* are formed from polymerization of nitriles:

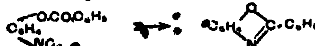


II. *Reduction Reactions.*—Mainly from the reduction of *o*-substituted nitro-benzenes; thus we have:

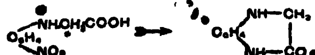
(*a*) *Indole* from *o*-nitrophenylacetaldehyde.



(*b*) *Benzoxazoles* from benzoyl-*o*-nitrophenols.

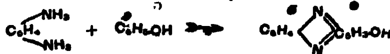


(*c*) Reduced *quinoxalines* from *o*-nitrophenyl-*a*-aminoacids.

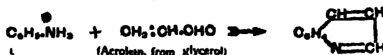


III. *Oxidation Reactions.*—These are not so common as the preceding, the chief are:

(*a*) *Phenazines* from *o*-diamines and phenols.



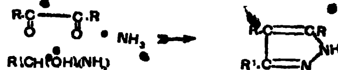
(*b*) *Quinolines* from aromatic amines and glycerol.



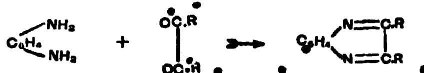
IV. *Condensation Reactions.*—These are by far the most numerous, and may be grouped as follows:

A. *From α-diketones.*

(*a*) *Glyoxalines,* with ammonia and aldehydes.

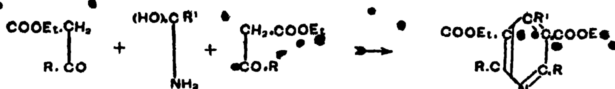


(*b*) *Quinoxalines,* with *o*-diamines.

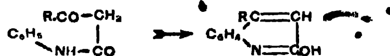


B. *From β-diketones.*

(*a*) *Pyridines,* with aldehyde ammonia.



(*b*) *Quinolines,* from anilides of β-keto-acids.

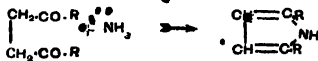


C. *From γ-diketones.*

(*a*) *Furfuranes.*

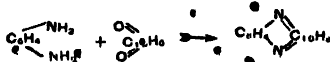


(*b*) *Pyrrols,* with ammonia.



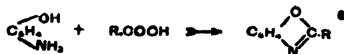
D. *From o-diamines.*

(*a*) *Phenazines,* with *o*-quinones.



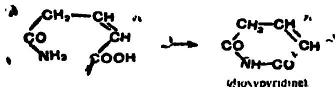
E. *From o-aminophenols.*

(*a*) *Benzoxazoles,* with fatty acids.

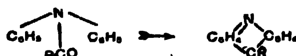


F. *From aminoacids.*

(*a*) *Pyridines*, from glutaconamic acids.

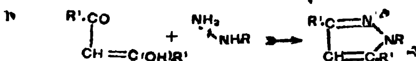


(*b*) *Acridines*, from diphenylacidamides.

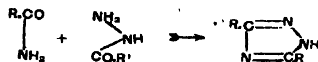


G. *From hydrazine.*

(*a*) *Pyrazoles*, from hydrazines and β-diketones.

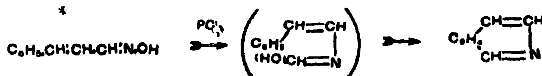


(*b*) *Triazoles*, from acid hydrazides and amides.



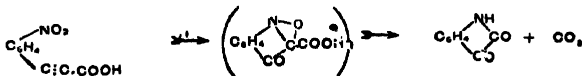
H. *From hydroxylamine.*

(*a*) *Isoquinoline*, from cinnamaldoxime.

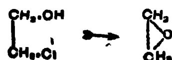


I. *Alkaline condensation or decomposition.*

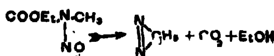
(*a*) *Isatin*, from *o*-nitrophenylpropiolic acid and alkali.



(*b*) *Ethylene oxide*, from chlorohydrin and alkali.



(*c*) *Diazomethane*, from nitrosomethylurethane and alkali.



CHAPTER II

THREE- AND FOUR-MEMBERED RINGS: ALKYLENE OXIDES, SULPHIDES AND IMIDES; ALIPHATIC DIAZOCOMPOUNDS

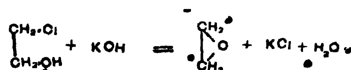
FROM what has already been said respecting the relative instability of tri- and tetra-atomic ring complexes, it will be surmised that the heterocyclic derivatives of these types are not very numerous. As a matter of fact, attempts to prepare different compounds of this kind have frequently resulted in polymeric products containing more stable ring systems. For example, ethylene sulphide, $S\Big\langle\begin{array}{l}CH_2\\ |\\ CH_2\end{array}$, has never been isolated, formation of the six-membered diethylene disulphide, $S\Big\langle\begin{array}{l}CH_2—CH_2\\ CH_2—CH_2\end{array}\Big\rangle S$, always taking place; and similarly, diazoacetic ester polymerizes very readily into tridiazoacetic ester, $COOEt.CH\Big\langle\begin{array}{l}N_2—CH.COOEt\\ N_2—CH.COOEt\end{array}\Big\rangle N_2$, which may contain either a six-membered or a nine-membered ring.

Consequently we need refer here merely to a few typical classes of these smaller ring systems, in which the individual members (with the exception of the aliphatic diazoderivatives) are of little general interest. We may classify these compounds as follows:—

(*a*) Alkylene oxides
(*b*) Alkylene sulphides and imides.
(*c*) Cyclic oxime derivatives.
(*d*) Aliphatic diazocompounds.

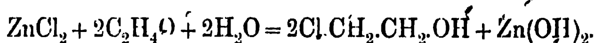
(*a*) **Alkylene Oxides.**—These bodies are internal ethers of the

glycols, and in many cases closely resemble ordinary aliphatic ethers. Thus *tetramethylene oxide* and *pentamethylene oxide* (which may be included here, although not belonging to the ring systems under discussion) are mobile, low-boiling liquids, formed respectively from the glycols $HO.[CH_2]_4OH$ and $HO[CH_2]_5OH$ upon heating the latter with sulphuric acid. This ready elimination of water recalls the ease with which acids such as succinic, phthalic, or camphoric yield cyclic anhydrides, and is no doubt due to the same cause, namely, the spacial proximity of the hydroxyl groups, for it is found that the lower members of the glycol series do not furnish their corresponding ethers by this means. However, it is possible to prepare *ethylene oxide* or *trimethylene oxide* from the monohalogen esters of the glycols by the action of caustic alkalies :



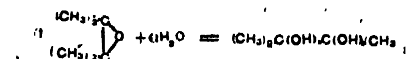
Ethylene oxide is an ethereal liquid, boiling at 13° C., and possessing a superficial chemical resemblance to its isomer acetaldehyde, $CH_3.CHO$. This is due to the fact that, whilst the residual affinity of the carbonyl group causes aldehyde to unite with (for example) ammonia or hydrocyanic acid, yielding the respective addition products $CH_3.CH\langle^{OH}_{NH_2}$ and $CH_3.CH\langle^{OH}_{CN}$, the "strain" in the triatomic ring complex produces a state of affairs very similar to unsaturation, and any opportunity to form open-chain addition products is eagerly seized. Consequently ammonia, hydrocyanic acid, and various other reagents react with ethylene oxide, the products in the first-mentioned instances being *oxethylamine*, $\begin{matrix} CH_2.OH \\ | \\ CH_2.NH_2 \end{matrix}$, and *hydracrylic acid nitrile*, $\begin{matrix} CH_2.OH \\ | \\ CH_2.CN \end{matrix}$. Similarly, it is gradually decomposed by water to re-form *glycol*, and, although neutral to litmus, will

slowly precipitate some metallic oxides from solutions of their salts. For instance,

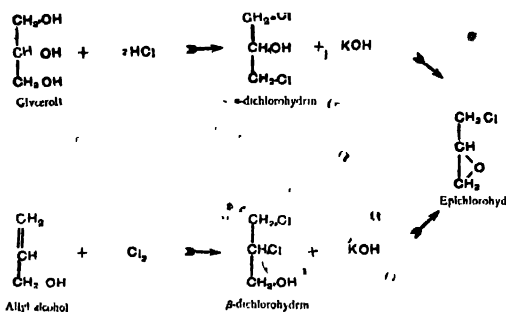


$$ZnCl_2 + 2C_2H_4O + 2H_2O = 2Cl.CH_2.CH_2.OH + Zn(OH)_2.$$

It is interesting to notice that, in accordance with the general rule that acid substituents conduce to ring stability, and conversely, *tetramethylethylene oxide* (which possesses no free hydrogen atoms attached to the cyclic carbon chain) unites vigorously with water, the product being *pinacone*:



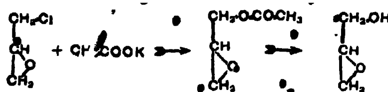
The only other alkylene oxides which need to be mentioned are the *epihalo-hydrins* and the *glycides*. If we act on either α- or β-dichlorohydrin with caustic potash, there results *epichlorohydrin*, a mobile, heavy liquid, boiling at 117° and resembling chloroform in smell and in its excellent solvent powers.



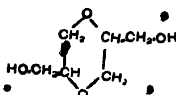
Epibromohydrin is similarly formed from the dibromohydrins, whilst *epiiodohydrin* may be produced from epichlorohydrin and potassium iodide.

Epichlorohydrin resembles ethylene oxide in many of its reactions, but does not suffer rupture of its triatomic ring system so readily; on the other hand, when heated with anhydrous potassium acetate, it exchanges its chlorine for the acetyl group,

and the *glycide acetate* so formed may then be hydrolysed to *glycide* or *epihydrin alcohol*:



If, however, an alcoholic solution of potassium acetate is used, polymerization to a more stable ring system takes place, and *diglycide acetate* is formed, which by saponification furnishes *diglycide*, probably



(*b*) **Alkylene Sulphides and Imides.**—Speaking in general terms, sulphur in organic compounds is more basic than oxygen, and nitrogen more so than either. It is therefore not surprising to learn that neither *ethylene sulphide*, $\begin{matrix}CH_2\\ \mid\ \ \ S\\ CH_2\end{matrix}$, nor *ethylene imide*, $\begin{matrix}CH_2\\ \mid\ \ \ NH\\ CH_2\end{matrix}$, is sufficiently stable to exist; these compounds are polymerized at the moment of their formation to *diethylene disulphide* and *piperazine*,* $NH\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}NH$, respectively. The tetra-atomic *trimethylene imide*, $CH_2\begin{matrix}CH_2\\ CH_2\end{matrix}NH$, is, however, fairly stable, and of course

* It is worthy of note that, although ethylene diamine hydrochloride yields only piperazine as stated above, Marckwald believes that *ethylene imide* is obtained from bromethylamine and silver oxide, since the product of this reaction (hitherto formulated as *vinylamine*, $CH_2{:}CH.NH_2$) gives a benzenesulphonyl derivative which is insoluble in alkalies, whereas all other compounds of the structure $R.NH.SO_2.C_6H_5$ dissolve in aqueous alkalies owing to the acidity of the hydrogen in the group $-NH.SO_2-$.

the higher homologues *pyrrolidine* and *piperidine* are well-defined organic bases (*cf.* pp. 53, 121). Moreover, if the other substituents of the heterocyclic atoms are sufficiently acidic in nature, stable derivatives of the triatomic systems are sometimes encountered; thus *tolane sulphide*, $C_6H_5.C\overset{S}{\triangle}C.C_6H_5$, is found amongst the products of the action of heat on dibenzyl sulphide, $C_6H_5.CH_2.S.CH_2.C_6H_5$, whilst certain compounds of the type $\begin{matrix}C_6H_5.CH:C \\ R.CO.N\end{matrix}\!\!>\!CO$, as well as the imide of oxalic acid, may possibly be related to the class of alkylene imides.

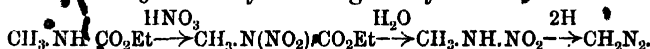
(*c*) **Cyclic Oxime Derivatives.**—It should be noted that the nitrogen alkyl ethers of the *syn*-aldoximes $\begin{matrix}R.CH \\ \| \\ NOH\end{matrix}$, are supposed by Hantzsch and Werner to possess the structure $\begin{matrix}R.CH \\ \mid \\ Alkyl\ N\end{matrix}\!\!>\!O$, *i.e.* are derived from the hypothetical system, $\begin{matrix}CH_2 \\ NH\end{matrix}\!\!>\!O$: Baeyer's *isatogenic ester*, $C_6H_4\!\begin{matrix}—CO \\ —N—O\end{matrix}\!\!>\!C.COOEt$, formed by the action of strong sulphuric acid upon *o*-nitrophenylpropiolic ester, is another example of this class.

(*d*) **Aliphatic Diazo-compounds.**—We come finally to the derivatives of the unknown *hydrazi-methane*, $\begin{matrix}NH \\ \mid \\ NH\end{matrix}\!\!>\!CH_2$. There are a few unimportant carboxylic derivatives of this substance, which are barely capable of existence in the free state, but by far the most interesting members of this group are *diazomethane*, $\begin{matrix}N \\ \| \\ N\end{matrix}\!\!>\!CH_2$, and its substitution products.

Diazomethane was first prepared in 1894 by von Pechmann by distilling nitrosomethylurethane with alcoholic potash:

$$CH_3.NH.CO_2Et \longrightarrow CH_3.N(NO).CO_2Et \longrightarrow CH_2N_2 + CO_2 + EtOH.$$

It may also be made by reducing methylnitroamine:

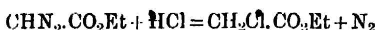


$$CH_3.NH.CO_2Et \xrightarrow{HNO_3} CH_3.N(NO_2).CO_2Et \xrightarrow{H_2O} CH_3.NH.NO_2 \xrightarrow{2H} CH_2N_2.$$

It is a pale yellow gas, remarkable for its poisonous nature and its capacity for acting as a methylating agent by elimination of nitrogen (it will be remembered that primary aliphatic diazonium salts similarly give up their nitrogen spontaneously, although aromatic diazocompounds are usually isolable). Thus it yields methyl alcohol with water, methyl esters with carboxylic acids, and methyl derivatives with phenols or primary and secondary amines.

Its *disulphonic acid* is produced as the potassium salt when potassium nitrite acts upon potassium aminomethanedisulphonate, $NH_2.CH(SO_3K)_2$.

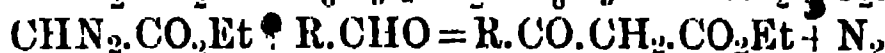
The action of nitrous acid upon glycocollester hydrochloride leads to the formation of *diazoacetic ester*, N:N>CHCOOEt (Curtius, 1883). The free acid decomposes at once into glycollic acid and nitrogen, but its salts, esters, and amide are fairly stable, although somewhat explosive. Its reactivity is similar to that of diazomethane; some typical decompositions are shown in the following equations:—



$$CHN_2.CO_2Et + HCl = CH_2Cl.CO_2Et + N_2$$

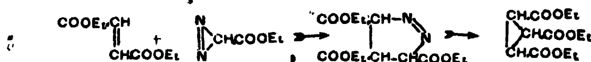


$$CHN_2.CO_2Et + C_6H_5.NH_2 = C_6H_5.NH.CH_2.CO_2Et + N_2$$



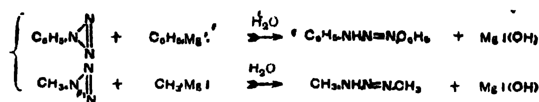
$$CHN_2.CO_2Et + R.CHO = R.CO.CH_2.CO_2Et + N_2$$

With ethylenic esters, *pyrazoline carboxylic esters* are formed, and on heating these nitrogen is eliminated and the corresponding *trimethylene carboxylic esters* are left:



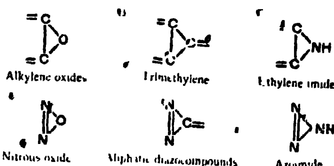
By heating diazoacetic ester with strong alkalies, the alkaline diazoacetates formed are polymerized to salts of *tridiazoacetic acid*, which yields *hydrazine* salts, N_2H_4, HX, on digestion with mineral acids (Curtius, 1894), and from the latter *azoimide* or hydrazoic acid, N:N>NH, may be obtained with nitrous acid.

Dimroth has recently prepared aliphatic diazoimide compounds from alkyl azoimides by means of the Grignard reagent; these are exceedingly soluble, unstable substances, and their formation may be compared with that of diazoamidobenzene from phenyl-azoimide.



The corresponding diazo-esters of propionic, succinic, etc., acids are also known.

It is of interest here to compare the series of known triatomic ring compounds of carbon and of nitrogen:



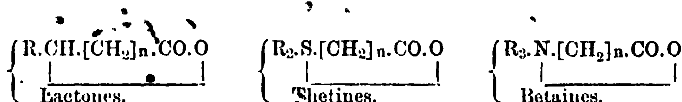
Reading from left to right, it is evident that the instability increases in the same order in each series, whilst the chemical reactivity increases progressively.

CHAPTER III

LACTONES, THETINES, AND BETAINES

I. GENERAL

IT is convenient next to describe a somewhat important group of compounds, many of which occur in nature, and which are made up of tetra-, penta-, hexa-, or hepta-heterocyclic systems. They may all be regarded as the internal anhydrides (or salts) of oxycarboxylic acids, and may be typically formulated as follows:—



It will thus be seen that the *methylene* group CH_2- in *lactones* is replaced by basic quadrivalent *sulphur* in *thetines*, and by basic quinquevalent *nitrogen* in betaines; moreover, as will be more fully emphasized in the following pages, the most stable *lactone* rings contain five or six atoms ("n": 2 or 3), whilst (except in the aromatic thetines and betaines) the two latter classes are usually derived from a four-membered heterocyclic system ("n": 1).

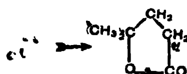
II. LACTONES

In 1879 Fittig prepared a mobile liquid of the molecular formula $C_6H_{10}O_2$, which dissolved slowly in cold aqueous alkalies, and was reprecipitated by acids: it appeared to be some kind of anhydride, but its properties did not permit of its

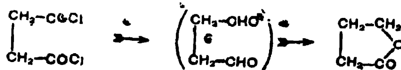
formulation as an ordinary acid anhydride, $(R.CO)_2O$, or a dilactide of the type R.CH(–O–)CO / CO–CHR. Accordingly, it was supposed to be $C_3H_7.CH{-}CH_2$ / O—CO, and this new type of internal anhydride or ester was christened "*lactone*." In confirmation of this view Fittig proved that by addition of hydrogen bromide to pyroterebic acid, $(CH_3)_2C{:}CH.CH_2.COOH$, and subsequent treatment with sodium carbonate the same compound was obtained.

In the following year, however, Erlenmeyer attempted to prepare a similar lactone from β-bromo-β-phenylpropionic acid, $C_6H_5.CHBr.CH_2COOH$, but only obtained styrolene. He was thus led to suggest that the same conditions which favoured anhydride formation of the ordinary type (*i.e.* a five-membered ring as in succinic anhydride) were necessary for lactone formation. Fittig's *isocaprolactone*, therefore, became $(CH_3)_2C{-}CH_2{-}CH_2$ / O—CO, and this view was supported by its formation in the oxidation of isocaproic acid (according to the "Markownikow rule," the carbon atom poorest in hydrogen would be first attacked):





Similarly, reduction of laevulinic acid, $CH_3CO.CH_2.CH_2.COOH$, led to the production of *γ-valero-lactone*, and directly afterwards Bredt showed that the product of reduction of succinyl chloride (already studied by Saytzew in 1873) was *γ-butyro-lactone*:

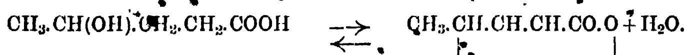


or more probably,



Lactones may be obtained by the following general reactions:—

1. Elimination of water from the corresponding oxy-acid:

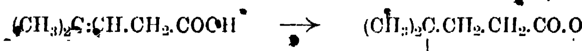


$CH_3.CH(OH).CH_2.CH_2.COOH \rightleftarrows CH_3.CH.CH.CH.CO.O + H_2O.$

This may be accomplished by heat, but frequently takes place on liberation of the acid from its salts; in such cases there is an equilibrium set up between acid and lactone (as shown in the equation), the proportion of lactone usually greatly preponderating.

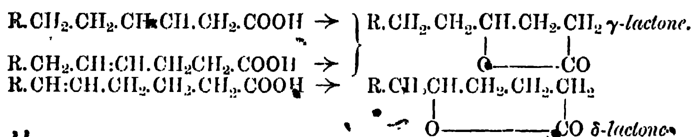
2. From unsaturated acids:

(*a*) By boiling with water, *e.g.*



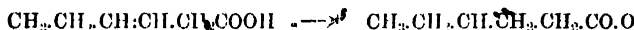
$(CH_3)_2C:CH.CH_2.COOH \rightarrow (CH_3)_2C.CH_2.CH_2.CO.O$

(*b*) By addition of hydrogen bromide and treatment of the product with alkaline carbonate; this is a very general reaction, and may lead to the following products:—



$R.CH_2.CH_2.CH:CH.CH_2.COOH \rightarrow$
$R.CH_2.CH:CH.CH_2CH_2.COOH \rightarrow$ } $R.CH_2.CH_2.CH.CH_2.CH_2$ (O—CO) *γ-lactone.*
$R.CH:CH.CH_2.CH_2.CH_2.COOH \rightarrow R.CH_2.CH.CH_2.CH_2.CH_2$ (O—CO) *δ-lactone.*

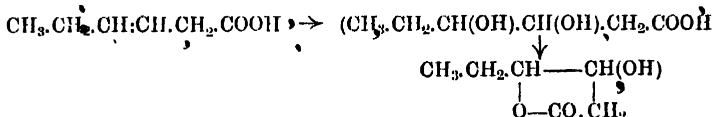
(*c*) By boiling with 50 per cent. dilute sulphuric acid, *βγ*- and *γδ*-unsaturated acids give *γ-lactones*, *e.g.*



$CH_3.CH_2.CH:CH.CH_2.COOH \rightarrow CH_3.CH_2.CH.CH_2.CH_2.CO.O$

βγ-Hydrosorbic acid. Caprolactone.

(*d*) By careful oxidation with dilute permanganate, the same acids give oxy-lactones; thus—

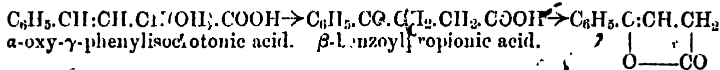


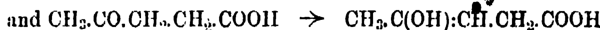
$CH_3.CH_2.CH:CH.CH_2.COOH \rightarrow (CH_3.CH_2.CH(OH).CH(OH).CH_2.COOH)$

$\downarrow$

$CH_3.CH_2.CH—CH(OH)$
$O—CO.CH_2$

(*c*) By isomerization of a few unsaturated oxy acids by heating; for instance,

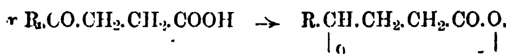




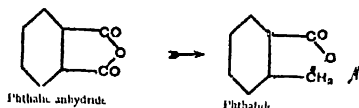
and $CH_3.CO.CH_2.CH_2.COOH \rightarrow CH_3.C(OH){:}CH.CH_2.COOH$



3. By reduction of ketonic acids with sodium amalgam:

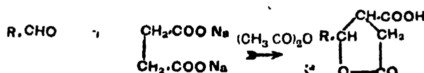


4. By reduction of acid chlorides (*cf.* p. 26) or anhydrides:



5. By condensation of aldehydes with sodium succinate in presence of acetic anhydride.

These products, known as *paraconic acids*, will be discussed shortly in greater detail.



Most of the aliphatic lactones are mobile liquids of fairly low boiling-point, readily miscible with most organic solvents. We may take the *γ-lactones* (the most stable members of the class) as typical of the chemical behaviour of these derivatives, and may further consider three general kinds of reaction:

I. *Opening of the Lactone Ring.*

On boiling with *water*, the conditions of equilibrium represented by



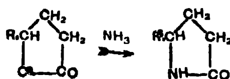
are altered, more free acid being formed, but it is exceptional for more than 20 per cent. of lactone to be decomposed, even at 100°. Aqueous *sodium*

carbonate reacts somewhat more readily, but it is necessary to use aqueous alkali hydroxides in order conveniently to obtain the theoretical amount of oxy-acid. *Sodium ethoxide*, on the other hand, will, under certain conditions, produce the ethyl ether of the corresponding oxy-acid,



$$R.CH(OC_2H_5)CH_2.CH_2.COONa$$

Ammonia always forms *lactams* from lactones, and is never known to rupture the ring-system:



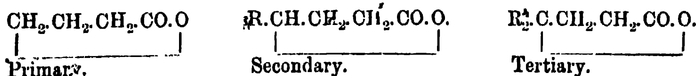
These compounds, which are also readily obtainable from γ- or δ-amino-fatty acids, are violent poisons.

Finally, *potassium cyanide* reacts with lactones to form the mono-nitriles of dibasic acids. It was in this way that Haller transformed campholide to homocamphoric acid, the calcium salt of which yields camphor on distillation:



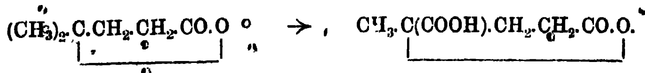
Halogen acids (especially HCl) react similarly, and produce chloro-fatty acids or esters.

II. *Oxidation*.—The behaviour of lactones upon oxidation varies according to the manner of substitution of the lactone ring. Thus we may classify lactones as follows:



$CH_2.CH_2.CH_2.CO.O$	$R.CH.CH_2.CH_2.CO.O.$	$R_2.C.CH_2.CH_2.CO.O.$
Primary.	Secondary.	Tertiary.

Of these, the tertiary group is most stable, and oxidizing agents merely attack one of the substituents, R.



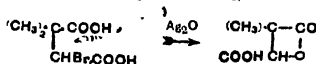
$$(CH_3)_2.C.CH_2.CH_2.CO.O \rightarrow CH_3.C(COOH).CH_2.CH_2.CO.O.$$

Primary and secondary lactones are usually completely broken up.

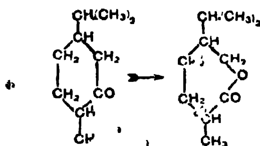
III. *Reduction.*—Simple lactones can be reduced in general only by phosphorus and hydriodic acid, the products being the simple fatty acids. Polyhydroxylated lactones, however, will sometimes reduce in alkaline media to corresponding oxy-aldehydes, and this has sometimes proved useful in synthetic work on the sugars.

There are a few individual lactones of special interest which we will now describe.

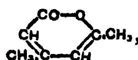
In accordance with the general applications of Baeyer's Strain Theory, there are very few β- or ε-lactones sufficiently stable to exist, whilst the δ-lactones (six-membered rings) are more easily decomposed than the γ-members. There are indeed only four β-lactones known—the three (*ortho-*, *meta-*, and *para-*) lactones prepared by Einhorn from the *nitro-β-phenyl-β-bromopropionic acids*, $NO_2.C_6H_4.CHBr.CH_2.COOH$, and one aliphatic member, obtained by Baeyer from *bromo-unsym-dimethyl succinic acid*—



The latter chemist has also prepared a few ε-lactones by the action of "Caro's acid" ($HO.O.SO_3.H$) on cyclic ketones; *e.g.*,



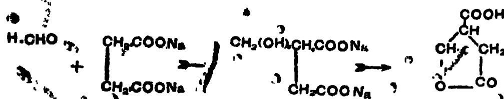
Campholide, which may be similarly obtained from camphor, and also by reduction of camphoric anhydride (p. 29), may be regarded as either a δ- or an ε-lactone.

Amongst *unsaturated lactones* we may notice the two *angelica lactones* from lævulinic acid (*cf.* p. 28): *parasorbic acid*, $CH_3.CH.CH_2.CH:CH.CO.O$, of which coumarin (p. 83) is a benzo-derivative, and *mesitenic lactone*, , obtained by Hantzsch in the reduction of acetoacetic ester.

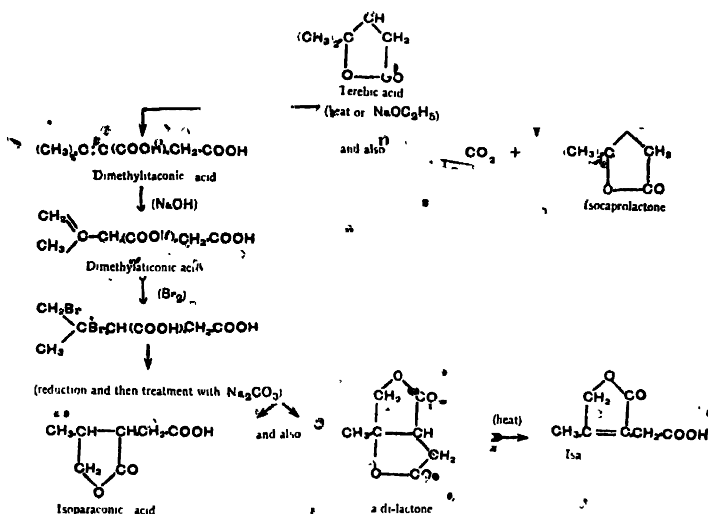
The last two compounds are α-pyrones (*cf.* p. 82).

A series of somewhat important lactone acids (which have been very thoroughly investigated by Fittig) may be obtained, as already explained, by an extension of Perkin's reaction, a mixture of an aldehyde and sodium succinate being heated for some hours with acetic anhydride. The formation

of the simplest member of this group, *paraconic acid*, will serve to explain the rest :

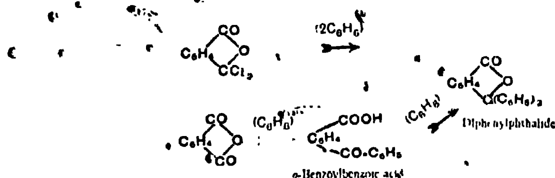


These acids undergo a variety of transformations by the application of heat, alkalies or other reagents, and are the more interesting since *dimethylparaconic* or *terebic acid* is one of the oxidation products of many terpenes. The following scheme illustrates the further decomposition of this compound, and will serve to give some idea of the general nature of Fittig's researches.

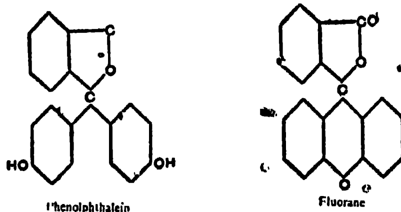


Phthalides and Phthaleins.—It will be recollected that γ-lactones can often be obtained by reduction of corresponding acid anhydrides; the substance thus prepared from phthalic anhydride, *phthalide*, $C_6H_4\langle{}^{CO}_{CH_2}\rangle O$, is of especial importance, both from a theoretical point of view and from its relationship to numerous important dyestuffs. Theoretically speaking, its derivatives form a kind of transition stage between the anhydride-like aliphatic lactones and the salt-resembling thetines or

betaines. The "basic" nature of the aliphatic carbon atom in triphenylmethane is well known, and if the hydrogen atoms of the methylene radicle in phthalide are replaced by aromatic residues, the basicity of the carbon atom concerned is so much strengthened that the oxy-acid $(C_6H_5)_2C(OH).C_6H_4.COOH$ exists only in the form of salts, which when acidified revert at once to *diphenylphthalide*, $C_6H_4\left<\begin{matrix}CO\\C(C_6H_5)_2\end{matrix}\right>O$. This compound can be synthesized by oxidizing triphenylmethane-*o*-carboxylic acid, and also by allowing aluminium chloride to act upon a mixture of benzene and phthalic chloride or anhydride :



If the intermediate product (*o*-benzoylbenzoic acid) in the latter reaction is heated with phenol and stannic chloride, *phenyl phenolphthalide*, $C_6H_4\left<\begin{matrix}CO\\C\end{matrix}\right>O$ with C_6H_5 and $C_6H_4.OH$ on the C, is formed, whilst, finally, if the methylene hydrogen atoms are replaced by phenolic groups, members of the *phthalein* series are formed. Thus by heating the requisite proportions of phthalic anhydride and phenol with zinc chloride the compounds



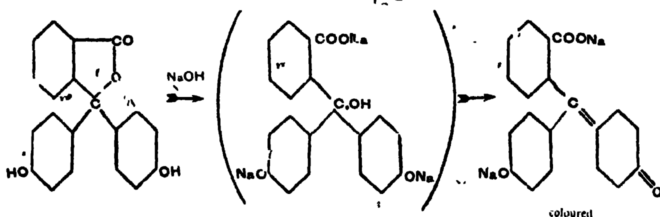
Phenolphthalein Fluorane

are formed, the former preponderating; the second compound

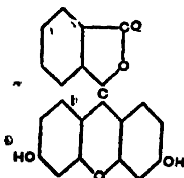
will be discussed more fully with the pyrones in Chapter VIII. (six-membered ring systems).

Phenolphthalein is almost colourless, but some of its salts are of a vivid red colour; hence its use as an indicator. The change in colour has been explained in two ways: one theory assumes that, whilst the lactone is colourless, the acid ion, $C_6H_4\begin{cases} COO^- \\ C(C_6H_4OH)_2OH \end{cases}$ is coloured (it is only the solutions in dilute alkali which are coloured, the lactone itself (nonionized) and solutions in strong aqueous alkali (which would diminish the amount of ionic dissociation of the alkaline salt) are colourless).

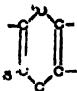
The other view is that the colour is due to a quinonoid structure in one part of the molecule, thus:

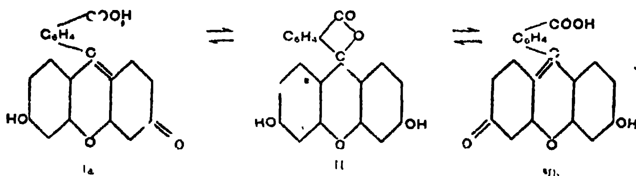


If resorcinol is substituted for phenol in the above preparation, *resorcinol-phthalein* or *fluorescein*, a yellowish-red compound soluble in strong aqueous alkalies to a dark red solution, results. This substance is strongly fluorescent in all solvents, and its structure has been proved to be:



In other words, this compound is also a derivative of *dibenzo-*

pyrone. The fluorescent nature of the fluoresceins has been explained by R. Meyer on the hypothesis that the system  is a *fluorophore*, i.e. is capable of showing fluorescence in presence of favourable substituents (*fluorogens*)—in this case the adjoining aromatic nuclei. On the other hand, Hewitt supposes that such substances owe their fluorescence to the capacity of the molecule to exhibit "double symmetric tautomerism." Thus it is argued that the fluorescence of the above compound is due to the vibration of the molecule through the following phases :



Neither phenolphthalein nor fluorescein are dyestuffs, but the following tetrasubstituted fluoresceins are vivid dyes,—not so much used at present as formerly, owing to their somewhat crude shades: *eosin* (tetrabromo-), *erythrosin* (tetraiodo-), and *safrosin* (dibromdinitro-).

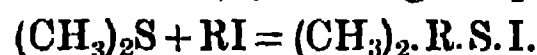
Mention must also be made of the *rhodamines*, which are fluorescent dyes derived from *m*-amino-phenols (instead of *m*-dioxybenzenes) and phthalic anhydride.

III. Thetines

The thetines (*thio-betaines*) may be regarded as thio-β-lactones of the general formula $R_2S.CH_2.CO.O$ (with a ring bond from S to O). It appears that the strongly basic nature of the quadrivalent sulphur atom is sufficient in this instance to overcome the usual reluctance of a tetra-atomic chain to form a ring-system, or, in other words, whilst the lactones are internal esters, the thetines and betaines (for exactly the same considerations apply to the nitrogen atoms in the latter class) are internal salts.

The aliphatic thetines were first prepared by Letts and Crum

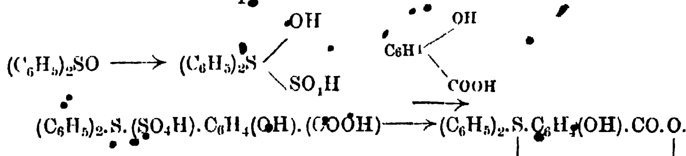
Brown in 1878, from alkyl suphides and halogen fatty acids. Dimethyl sulphide, although not a base in the strict sense of the word, is sufficiently basic to unite with alkyl halides (especially in presence of mercuric iodide) yielding sulphonium iodides:


$$(CH_3)_2S + RI = (CH_3)_2.R.S.I.$$

Similarly, from bromacetic acid and dimethylsulphide, the compound $(CH_3)_2.S(Br)CH_2.COOH$ (a *sulphonium bromide*) is produced, and is transformed by silver oxide to *dimethyl thetine*, $(CH_3)_2.S.CH_2.CO.O$, a deliquescent body crystallizing with one molecule of water, but neutral to litmus, and possessing all the characteristic properties of an internal salt, yet still sufficiently basic to yield normal sulphonium salts with strong acids.

It should be remembered that by means of the thetines sulphur has been obtained in the optically active state, for, starting from methylethyl sulphide, methylethyl thetine was prepared and resolved into its optically active constituents by means of *d*-bromo-camphorsulphonic acid. A better method, however, is to condense the same sulphide with ω-bromacetophenone, and to resolve the resulting *methyl ethyl phenacylsulphonium bromide*, $(CH_3)(C_2H_5)(C_6H_5.CO.CH_2)S.Br$, which contains no free carboxyl group, and is consequently a somewhat stronger base.

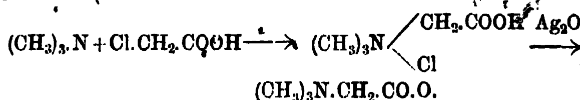
A few aromatic thetines have been prepared by Smiles by condensing aromatic sulphoxides with salicylic acid by means of cold concentrated sulphuric acid.



IV. Betaines

It follows from the preceding section that the betaines are derived from the system $\begin{matrix} R_3N—CH_2 \\ | \quad\; | \\ O—CO \end{matrix}$. The parent substance derives

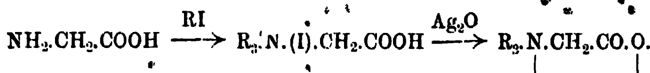
its name from *Beta vulgaris* (common beetroot), in which it was discovered by Scheibler in 1869. In the same year Liebreich synthesized it by a reaction similar to that used later in the preparation of thetines, namely :—



$$(CH_3)_3.N + Cl.CH_2.COOH \longrightarrow (CH_3)_3N\begin{matrix}/CH_2.COOH \\ \backslash Cl\end{matrix} \xrightarrow{Ag_2O} (CH_3)_3N.CH_2.CO.O.$$

He also prepared it by the oxidation of *choline* (p. 39).

Hofmann showed that tertiary amines and chloroacetic ester readily react, and that the products when treated with silver oxide yield *betaines*, and that these are also the result of exhaustive alkylation of glycocoll :

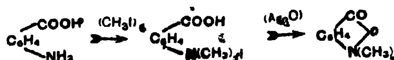


$$NH_2.CH_2.COOH \xrightarrow{RI} R_3.N.(I).CH_2.COOH \xrightarrow{Ag_2O} R_3.N.CH_2.CO.O.$$

Like the corresponding thetines, the betaines are weak bases, forming characteristic salts, with mineral acids, chloroplatinic acid, picric acid, etc. They are usually crystalline, and sometimes contain a molecule of water, which is expelled on heating to 100° ; in these cases it is difficult to say with certainty whether the crystallized compound is the free base-acid, $R_3N(OH).CH_2.COOH$, or whether it is merely a case of "water of crystallization."

Many of the aliphatic betaine derivatives occur in nature. A few of these are discussed in the concluding section of this chapter (p. 39).

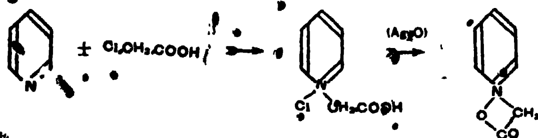
A few *aromatic betaines* have been synthesized, notably by methylating anthranilic acid derivatives :



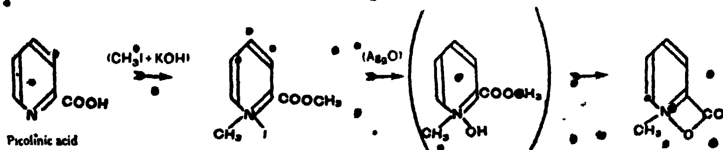
A *triphenylphosphorbetaine* is produced by the action of alkalies on the addition product of triphenylphosphine, $(C_6H_5)_3P$, and chloracetic acid.

Pyridine betaines are also of some importance ; the simplest member was

prepared by Vongerichten by the addition of chloracetic acid to pyridine (p. 103).



Hantzsch showed that similar products could be obtained by methylation of pyridinecarboxylic acids. For example:

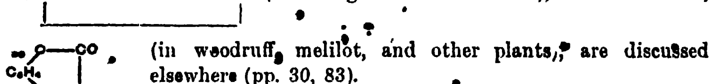


Some of these compounds also occur in plants (*cf.* p. 40).

V. Naturally occurring Lactones and Betaines

The members of these classes which are found in nature (most frequently in the vegetable kingdom) may best be classified for the present purpose according to the complexity of their structure.

(i) *Simple Lactones.*—The two most important members, *parasorbic acid*, $CH_3.CH.CH_2.CH:CH.CO.O$ (occurring in rowan berries), and *coumarin*,



(in woodruff, melilot, and other plants), are discussed elsewhere (pp. 30, 83).

(ii) *Complex Lactones.*—The constitutions of *santonine*, $C_{15}H_{18}O_3$ (from the buds of foreign species of the wormwood plant), and of *sedanolide*, $C_{12}H_{20}O_3$ (found in oil of celery), have only been ascertained comparatively recently, and are therefore of some interest.

The former compound was first isolated in 1830, but its structure was unknown until worked out by Cannizzaro and Andreocci some fifteen years ago. It is an excessively poisonous drug, is optically active, and is useful in medicine. On exposure to light, however, it is changed into *photosantonine*, which possesses no marked therapeutic properties. The main points in the proof of its structure are:

(*a*) It contains a carbonyl group =CO.

(*b*) With alkalies, salts of *santoninic acid*, $C_{15}H_{20}O_4$, are produced. The acid reverts to santonine on heating.

Santonine is therefore a *keto-lactone*.

(*c*) Oxidation and reduction reactions show it to be a *reduced dimethyl-naphthalene* derivative.

(*d*) By reduction with phosphorus and hydriodic acid, a *phenol-acid* is produced, which may be further changed into a *dimethyl-β-naphthol*.

(*e*) By distillation of *santonamine hydrochloride* (from the reduction of *santonine oxime*), a substance, *hyposantonine*, is formed, which yields a *dimethyl-phthalic acid*, which in turn may be converted to *p-xylene*.

$$\underset{C_{15}H_{18}O_3}{\text{Santonine}} \xrightarrow{(NH_2OH)} \underset{C_{15}H_{18}O_2(N.OH)}{\text{Oxime}} \xrightarrow{(\text{reduce})} \underset{C_{15}H_{19}O_2.NH_2}{\text{Santonamine}} \xrightarrow{(HCl.\text{Salt})} (\text{heated})$$

$$\underset{C_{15}H_{..}O_2}{\text{Hyposantonine}} \xrightarrow{(\text{oxidize})} \text{Dimethyl o-phthalic acid } (CH_3)_2C_6H_2(COOH)_2 \xrightarrow{\text{distil with CaO}} p\text{-Xylene } CH_3C_6H_4CH_3$$

The *dimethyl-β-naphthol* is therefore : [naphthalene ring with CH_3, OH, CH_3]

(*f*) Since *hyposantonine* (still containing a hydronaphthalene ring) can be transformed to a naphthalene derivative which is optically active, the source of optical activity lies in a side chain, and not in the reduced naphthalene group.

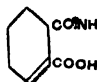
(*g*) Since a *phthalic acid*, and not a tetracarboxylic acid, is produced by oxidation of santonine, the lactone ring must be attached to that part of the naphthalene nucleus which does not contain methyl groups.

(*h*) By consideration of the compounds formed by the action of light on santonine, it has been shown that the carbonyl group forms part of the reduced dimethylnaphthalene ring, and that the most probable formula is accordingly—

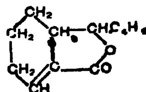
[structural formula: CH_3, C, CO, C, CH_2, $CH-CH.CH_3$, CO, CH_2, C, $CH-O$, CH_2, C, CH_3]

The constitution of *sedanolide* is much more simple. On gentle oxidation it gives *n-butyl phthalide*, $C_6H_4\langle{}^{CH.C_4H_9}_{CO}\rangle O$ whilst alkalies transform it to salts of

sedanolic acid, an oxy-acid which contains two atoms of hydrogen less than a ketonic acid, *sedanonic acid*, which is always found with sedanolide. Now, since both these acids furnish by reduction the same fully-reduced alcohol acid, it follows that the structure of sedanonic acid will give the clue to that of sedanolide. When the oxime of the latter acid is submitted to the "Beckmann rearrangement,"* the *mono-n-butylamide* of

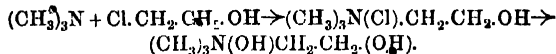
Δ^2-*tetrahydrophthalic* acid, 

, is formed.

Sedanolide is therefore 

(iii) *Compounds related to Betaine.*—It has already been pointed out that betaine itself occurs in beetroots. A number of its reduction products are also found in nature, and some of these, although not true betaines, may be mentioned here.

For example, the alcohol which corresponds to betaine, *choline* $(CH_3)_3N(OH).CH_2.CH_2(OH)$, occurs in nerve tissue, yolk of egg, etc., in the form of *lecithins* (complex glycerides of higher fatty acids and phosphoric acid). It was synthesized by its discoverer (Strecker, 1862):



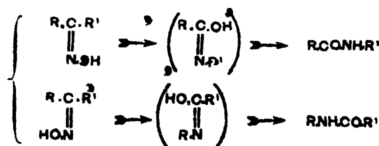
$$(CH_3)_3N + Cl.CH_2.CH_2.OH \rightarrow (CH_3)_3N(Cl).CH_2.CH_2.OH \rightarrow (CH_3)_3N(OH)CH_2.CH_2.(OH).$$

Boiling baryta dehydrates choline and forms the poisonous *neurine*, $(CH_3)_3N(OH).CH{:}CH_2$, which is present in decaying meat. (Choline and betaine are, however, non-poisonous.) Neurine is also formed when silver oxide acts upon the addition product of trimethylamine and ethylene dibromide $(CH_3)_3N(Br).CH_2.CH_2.Br$.

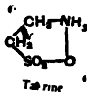
Again, the aldehyde intermediate between choline and betaine, $(CH_3)_3N(OH).CH_2.CHO$, is probably identical with *muscarine*, which occurs in certain plants.

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* The "Beckmann rearrangement" is the term given to the transformation undergone by many oximes in presence of sulphuric acid or phosphorus oxychloride, whereby derivatives of acid amides are formed:

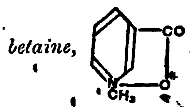


Finally, a very important animal product, *taurine*, known since 1824, and synthesized by Kolbe in 1862 by the action of ammonia on chlorethylsulphonic acid, $Cl.CH_2.CH_2.SO_3H$, is a sulphonic acid analogue of betaine :





(iv) *Pyridine Betaines.*—*Trigonelline*, occurring in goat's-horn, a plant nearly allied to clover, has been synthetically shown to be *methylnicotinic betaine*,



Apophyllenic acid does not occur free, but is one of the oxidation products of the opium alkaloid *narcotine*; since it is obtained by the action of silver oxide on the product of methylation of *cinchomeronic acid*, , it is also a pyridine betaine.

Arecoline and *arecaidine*, found in betel-nuts, are respectively the methyl ester and the free acid derived from (N-methyl tetrahydropyridine-β-carboxylic acid).

Pilocarpine, $C_{11}H_{16}O_2N_2$, which is found in Jaborandi leaves, was at one time thought to be a pyridine betaine, but more recently has been shown to be a *lactonic* derivative of *glyoxaline*, under which latter heading it will be described (p. 74).

CHAPTER IV

FIVE-MEMBERED RINGS: MONOHETEROCYCLIC SYSTEMS (FURFURANE, THIOPHENE, PYRROL, AND ALLIED COMPOUNDS)

I. General

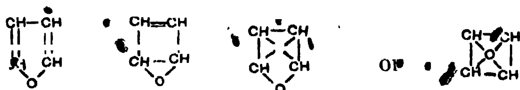
We have to deal in this chapter with a more distinctively heterocyclic series of compounds than those just discussed; that is to say, whereas the lactones and related compounds all partake in some measure of the nature of anhydrides, and their ring-systems can be opened and closed by more or less reversible reactions, the heterocyclic systems

```
C—C      C—C      C—C
‖  ‖     ‖  ‖     ‖  ‖
C  C  ,  C  C  ,  C  C
 \/       \/       \/
 O        S        NH
```

each persist through an entire series of chemical changes, each system behaving as a chemical entity, and if the heterocyclic ring is once broken, it cannot be readily reformed.

Moreover, the heterocyclic element—O, S, or NH—in these compounds is entirely abnormal in its behaviour: the oxygen is neither ethereal, ketonic, nor lactonic; the sulphur is chemically inactive, and, although apparently bivalent, is quite as stable as when in a sexavalent condition (*i.e.* as the sulphones); the secondary amino-group is hardly basic at all, and even functions as a "phenol," the imino hydrogen being replaced by metals. Finally, the physical properties of these elements which can be numerically estimated (*e.g.* refractive power or heat of combustion) are also abnormal here, and it has been variously

thought that the systems in question may best be represented either as:



Some of these derivatives have been known for many years: pyrrol was discovered in coal-tar by Runge in 1834, pyromucic acid by Scheele in 1780, and furfural by Döbereiner in 1831. However, their mutual relationships, together with those of the coumarones, indigo, carbazole, etc., were not recognized till very much later, the greater part of this work of systematization being carried out, notably by Baeyer, V. Meyer, and Knorr, between 1880 and 1890.

There are a few general methods of synthesis applicable to members of each series. Thus, γ-diketones (R.CO.CH_2.CH_2.CO.R), and mucic and saccharic acids, COOH.$[CH.OH]_4$.COOH, all undergo the following transformations:

(*a*) Distilled with P_2O_5, *furfurane* derivatives, CH=CH / CH=CH >O result.

(*b*) ,, ,, P_4S_6, *thiophene* ,, CH=CH / CH=CH >S

(*c*) ,, ,, NH_3, *pyrrol* ,, CH=CH / CH=CH >NH ,,

The reactions (*b*) and (*c*) also occur with the anhydrides of the succinic acid series.

Many of the corresponding compounds in all three series show a remarkable chemical (and occasionally physical) resemblance to each other, and also to the corresponding benzenoid compounds, as is shown in the table below. All three series, too, have their distinctive colour-reactions. Thus, with isatin or phenanthraquinone and concentrated sulphuric acids, the

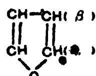
following colours are produced on addition of a compound of—

Furfurane	Violet.
Thiophene	Intense blue.
Pyrrol	Indigo blue.

Again, if a pine-shaving moistened with hydrochloric acid is placed in the vapours of these substances, it assumes the following colours:

Furfurane compound present . .	Green.
Pyrrol ,, ,, . .	Brilliant red.

It will have been noticed that, according to the formulation

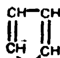


, two mono-substitution products (α and β) should exist, and this isomerism has been definitely observed in the pyrrol and indol series; with some of the furfuranes and thiophenes, however, the difference in properties between the α and β-isomers is so very slight that doubt has been expressed as to their distinct existence; and in view of this and of the above-mentioned abnormal character of the heterocyclic atoms, the symmetrical formula IV. (p. 42) has been put forward, but the point is not yet definitely settled.

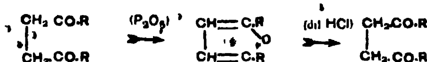
The following table shows the similarity of benzenoid, furfurane, thiophene, and pyrrol compounds, and emphasises the especially close coincidence between thiophene and benzene derivatives:—

Derivatives of:	Benzene.	Furfurane.	Thiophene.	Pyrrol.
R.H	B.p. 80°.	B.p. 32°.	B.p. 81°.	B.p. 131°.
$R.CH_3$	Toluene, b.p. 110°.	B.p. 63°.	Thiotolene, B.p. 113°.	B.p. 143°.
R.CHO	Gives Cannizzaro reaction. B.p. 179°.	Gives Cannizzaro reaction. B.p. 162°.	Gives Cannizzaro reaction. B.p. 198°.	—
R.CO.OH	By oxidation of benzaldehyde. M.p. 122°.	By oxidation of furfuraldehyde. M.p. 134°.	By oxidation of thiophenaldehyde. M.p. 126°.	M.p. 192°.
R.CO.R	B.p. 307°. From benzene and carbonylchloride.	—	B.p. 326°. From thiophene and carbonylchloride.	From pyrrol and carbonylchloride.
R.CH:CH.COOH	M.p. 133°. From benzaldehyde, sodium acetate, and acetic anhydride. Occurs in two forms.	M.p. 141°. Occurs in two forms.	M.p. 138°. From thiophenaldehyde, sodium acetate, and acetic anhydride.	—

II. DERIVATIVES OF FURFURANE



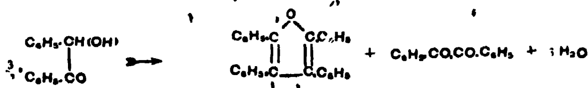
The furfurane group is perhaps less important than either of the others, but is nevertheless very interesting by reason of its close connexion with both the aliphatic and aromatic series. Thus when the α-disubstituted furfuranes are heated with aqueous hydrochloric acid under pressure, those γ-diketones from which they are formed by dehydration are regenerated:



The parent member, *furfurane*, was first prepared by Limpricht in 1870 by distilling barium pyromucate $(C_4H_3O.CO_2)_2Ba$; this is analogous to the formation of benzene on distilling calcium benzoate, $(C_6H_5.CO_2)_2Ca$.

It is also formed when pine-shavings are distilled, and is a low-boiling liquid with a characteristic smell; the oxygen therein cannot be recognized by any of the reactions usually shown by that element when present in organic radicles.

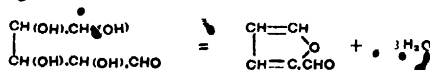
Tetraphenylfurfurane is interesting because of its formation from benzoin on treatment with hydrochloric acid in sealed tubes:—



The only other furfurane derivatives we need mention are *α-furfuraldehyde* and a few of the *carboxylic acids*.

The former substance occurs in the products of destructive distillation of wood, sugars, or bran (the group-name is derived from the latter method of formation: Latin *furfur*, bran). Pentoses are quantitatively converted to furfuraldehyde by

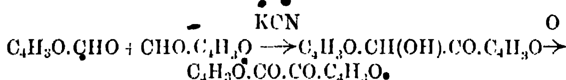
distillation with hydrochloric acid, and are often estimated in this way:



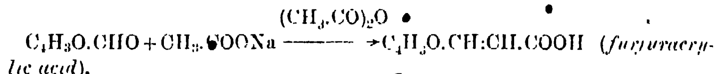
Furfuraldehyde possesses a close chemical resemblance to benzaldehyde; it forms exactly similar addition compounds (oximes, cyanhydrin, etc.), and its other reactions are also exactly parallel with those of the aromatic compound, as the following examples show:--

(*a*) With concentrated potash, a mixture of *furfuryl alcohol* and *potassium pyromucate* is produced.

(*b*) Alcoholic potassium cyanide catalytically condenses it to *furoin* (analogue of benzoin), from which *furil* results by oxidation:



(*c*) It condenses with fatty acid salts in presence of acetic anhydride (Perkin's reaction):



The best-known furfurane acid is *pyromucic acid*, discovered by Scheele in 1780, in the distillation of mucic acid. Its structure and relation to furfuraldehyde were determined by Baeyer. Its constitution follows from that of the latter substance (which is known by its indirect transformation into acetone diacetic acid), since it may be produced therefrom by simple oxidation or from its nitrile, which can be obtained in the usual way by dehydration of *furfuraldoxime*.

Some of the *a-dialkylfurfurane carboxylic acids* are also of great interest, since they are frequently formed in the distillation of tartaric and other aliphatic polyoxy-acids. For example, *pyrotritartaric acid* (aa^1-dimethylfurfurane-β-carboxylic acid) is thus obtained from tartaric acid, and may be synthesized from acetonylacetoacetic ester, as well as by elimination of CO_2 from some other synthetic acids; whilst it may be decomposed again in

under suitable conditions, either into a diketone or into a furfurane, as shown below :

$3\ C_4H_6O_6$ (Tartaric acid) $\xrightarrow{(-H_2O,\ CO_2)}$ $3\ CH_3CO.COOH$ (Pyruvic acid) $\xrightarrow{(heated)}$

$CH_3.CO.CH_2.COOEt$ + $Cl\ CH_2.CO.CH_3$ $\longrightarrow$ $COOEt.C{=}C.CH_3$ / $CH{=}C(OH).CH_3$ (Acetonylacetoacetic ester) $\xrightarrow{(H_2O)}$

$CH_3.CO.CH.COOEt$ / $CH_3.CO.CH.COOEt$ (Diacetosuccinic ester) $\xrightarrow{(CH_3CO)_2O}$ $COOH.C{=}C.CH_3$ / $COOH.C{=}C.CH_3$ (Carbopyrotritartaric acid) $\xrightarrow{(-CO_2)}$

$CH_2.COONa$ / $CH_2.COONa$ + $HO.C.CH_3$ / $H\ C.COOEt$ $\xrightarrow{(CH_3CO)_2O}$ $COOH.C{=}C.CH_3$ / $H\ C{=}C.CH_2.COOH$ (Methronic acid) $\xrightarrow{(-CO_2)}$

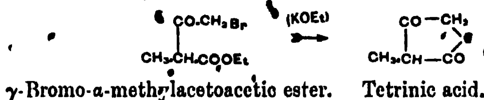
$CH_2.CO.CH_3$ / $CH_2.CO.CH_3$ (Acetonylacetone) + CO_2 $\xleftarrow{(H_2O\ at\ 160°)}$

$CH{=}C.CH_3$ / $COOH.C{=}C.CH_3$ (Pyrotritartaric acid) $\xrightarrow{(distilled)}$ $CH{=}C.CH_3$ / $CH{=}C.CH_3$ (Dimethylfurfurane) + CO_2

Finally, we come to *tetrahydrofurfurane* or *tetramethylene oxide*, $CH_2{-}CH_2$ / $CH_2{-}CH_2$ >O, (p. 19), which has not yet, however, been prepared directly from furfurane; and to the *ketotetrahydrofurfuranes*, some of which, like butyrolactone $CH_2{-}CH_2$ / $CH_2{-}CO$ >O, and succinic anhydride, $CH_2{-}CO$ / $CH_2{-}CO$ >O, are quite well known aliphatic compounds. The isomeric diketo compound, $CO{-}CH_2$ / $CH_2{-}CO$ >O, is also known having been synthesized from dibromacetoacetic ester :—

$CO.CH_2Br$ / $CHBr.COOEt$ $\xrightarrow{(heated)}$ $CO{-}CH_2$ / $CHBr{-}CO$ >O $\xrightarrow{(sodium\ amalgam)}$ $CO{-}CH_2$ / $CH_2{-}CO$ >O

The methyl derivative of this body was known earlier, and had received the name *tetrinic acid*, owing to its salt-forming properties. It had been prepared by a somewhat similar method:

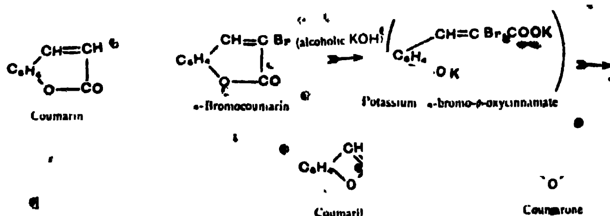


γ-Bromo-α-methylacetoacetic ester. Tetrinic acid.

Accordingly, the former compound was called *tetronic acid*, although its lactonic structure had in the meantime become apparent. The metallic salts of these derivatives are usually represented by means of the corresponding di-enolic formula.

The monobenzofurfuranes, [structure], are more usually called *coumarones*, a name given to them by Fittig, who obtained them in 1883 from the corresponding *coumarins* (six-membered α-pyrones, p. 83).

This conversion of a six-membered into a five-membered system is of interest from the point of view of ring-stability; we have already seen that many three-membered systems rearrange themselves to the corresponding six-membered ones with the utmost ease, and other examples of this kind which will be found in succeeding pages show that the most stable compound in any given case is not necessarily that in which there is least mechanical "strain," but that ring-stability in the heterocyclic series is also considerably affected by the chemical nature of the substituting groups. The mechanism of the present reaction probably involves intermediate formation of the *o*-oxy-cinnamic acids of which the coumarins are the lactones:—



Two other synthetic methods of formation of the *coumarones* (the parent member of which is a liquid somewhat similar to furfurane, and boiling at 169°) may be described:—

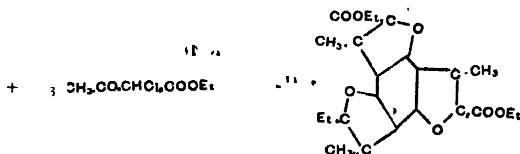
(*a*) from *o*-oxy-ω-chlorostyrolene and caustic alkali:



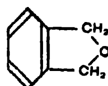
(*b*) from phenols and α-chloracetoacetic esters (Hantzsch):



With polyhydric phenols, benzopolyfurfurane derivatives may be produced, as, for example, from phloroglucinol:



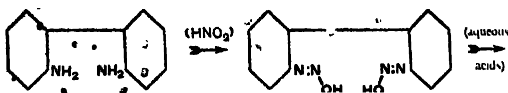
For purposes of classification, the *phthalides* and *phthalic anhydrides* are sometimes regarded as derived from a reduced "isobenzofurfurane,"

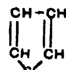


, but it may be pointed out that this is only true if we adopt a modified centric formula for furfurane, since *isobenzofurfurane* cannot be formulated on the Kekulé hypothesis:



We have seen that *benzo-poly-furfuranes* are formed synthetically from polyhydric phenols, and similarly we have *dibenzofurfurane*, more usually termed *diphenyleneoxide*, which is produced when diphenyl ether is passed through a red-hot tube, and is synthesized from *o*, *o*-didiazo-diphenyl salts:

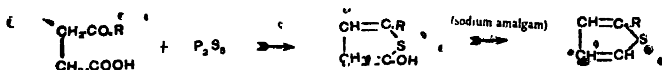


III. DERIVATIVES OF THIOPHENE, 

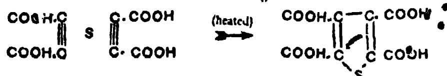
Thiophene compounds are obtained instead of furfuranes in nearly all the reactions in which the latter are produced by destructive distillation, if the operation is conducted in presence of phosphorus tri-sulphide, P_4S_6. Thus mucic acid yields thiophene carboxylic acid when heated with P_4S_6, instead of pyromucic acid, as on p. 46.

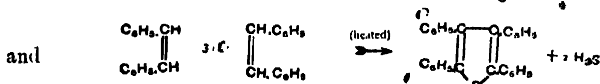
Two other methods of formation are also used:—

(a) γ-ketonic acids heated with phosphorus pentasulphide give *oxythiophenes*:



(b) Many ethylenic and acetylenic compounds form thiophene derivatives when heated with sulphur. For instance,



and 

The latter compound, *thionessal*, was first obtained from stilbene by Laurent in 1844, but was not recognized as a thiophene until nearly fifty years later.

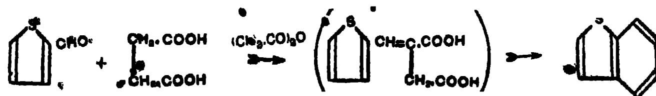
As a matter of fact, the history of the thiophene compounds as such dates only from about 1883, when V. Meyer showed that benzenes prepared from coal-tar contain traces of the corresponding thiophene compounds, which resemble them remarkably closely in nearly all physical properties, even as far as smell and boiling-point. Thus benzene and thiophene both boil at about 80°, and cannot be separated by physical means (advantage is taken of the more rapid sulphonation of thiophene in order to remove it from commercial benzene). Thiophene was in consequence so completely overlooked that its blue coloura-

tion with isatin and strong sulphuric acid passed as a test for benzene until Meyer found that benzene prepared from benzoic acid never gave the reaction, and was thus led to the discovery of the thiophenes and their relation to furfurane and pyrrol.

The table already given (p. 44) emphasizes the physical resemblance of the thiophenes to the benzenes: it must be added here that, by means of the same reactions which are used for the synthesis of aromatic compounds (halogenation, sulphonation, the Friedel-Crafts and Fittig syntheses of alkyl benzenes, preparation of benzoic acids, etc.), the corresponding thiophene derivatives may always be obtained. Usually, however, substitution proceeds more readily in the thiophene series. On the other hand, although thiophene is thus more reactive than benzene, the sulphur atom present is far less reactive than in corresponding dialkylsulphides, and can be converted from the bivalent to the quadrivalent or sexavalent condition neither by oxidation nor by addition of alkyl iodides. Moreover, Brühl has shown that the refractive power of thiophene is markedly less than that expected of a body containing a conjugated unsaturated system such as CH:CH.S.CH:CH, and evidently the nature of the intramolecular structure of this ring-system (as well as those of furfurane and pyrrol) is at present by no means thoroughly understood.

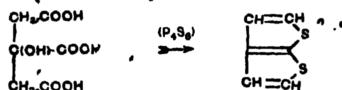
Derivatives of *selenophene*, CH-CH / ‖ ‖ / CH CH / Se, have been prepared by the action of phosphorus selenide on γ-diketones.

A few *benzothiophenes* are known, of which the parent member, *thionaphthene*, $C_6H_4<^{CH}_{S}>CH$, and *oxythionaphthene*, $HO.C_6H_3<^{CH}_{S}>CH$, are the most important; the latter has been synthesized from thiophenaldehyde and succinic acid:



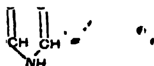
These compounds closely resemble naphthalene and α-naphthol respectively (see also *thioindigo*, p. 61).

Dithiophene or *thiophthene* is produced by distilling citric acid with P_4S_6:—



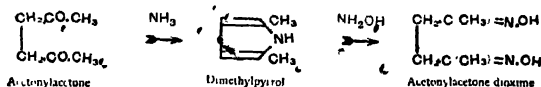
and *dibenzothiophene* (*diphenylene sulphide*) is formed similarly to diphenylene oxide, namely, by the action of a red heat upon *diphenylsulphide*. The sulphur in dibenzothiophene may be oxidized to a sulphone, although, as stated above, no thiophene sulphone is known.

IV. Derivatives of Pyrrol,



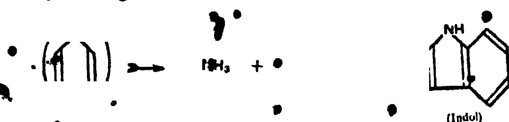
Just as the sulphur and oxygen atoms in thiophene and furfurane are quite abnormal in chemical behaviour, so the imino-group in pyrrol, instead of resembling those in ordinary secondary amines, is very weakly basic indeed, and frequently acts more like a phenolic group with an acidic hydrogen atom.

The pyrrols are obtained by the action of ammonia on γ-diketonic compounds, and, like the furfuranes, revert to these under special conditions. Thus we have—



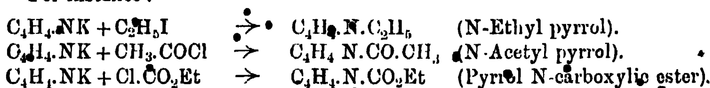
Pyrrol itself is a pleasant-smelling oil which occurs to a small extent in the distillates from coal-tar, bone oil, or peat. It may be synthesized by distilling the ammonium salt of mucic acid, by the reduction of succinimide with zinc or sodium, and by passing acetylene and ammonia through a red-hot tube.

Pyrrol forms salts with strong acids, at the same time undergoing polymerization to solid *tripyrrol*, which, when heated, yields benzopyrrol (indol), pyrrol, and ammonia.



Potassium (but not sodium) replaces the imide hydrogen in pyrrol, forming crystalline *potassium-pyrrol*, $C_4H_4.NK$; this compound reacts with a large number of organic halogen compounds, and thus produces N-derivatives of pyrrol.

For instance :



$C_4H_4.NK + C_2H_5I \rightarrow C_4H_4.N.C_2H_5$ (N-Ethyl pyrrol).
$C_4H_4.NK + CH_3.COCl \rightarrow C_4H_4\,N.CO.CH_3$ (N-Acetyl pyrrol).
$C_4H_4.NK + Cl.CO_2Et \rightarrow C_4H_4.N.CO_2Et$ (Pyrrol N-carboxylic ester).

The *C-alkyl pyrrols* are made by the usual synthetic methods. Many of the halogen derivatives of the pyrrols are unstable, but *tetraiodopyrrol* (*iodol*), $C_4I_4.NH$, which is produced by the action of alkaline iodine solutions upon pyrrol, resembles iodoform in appearance and in antiseptic properties.

The *carboxylic acids* of pyrrol are interesting, both from their chemical resemblance to phenol carboxylic acids and also as intermediate products in the synthesis of pyrrols, which usually result from them by the application of heat.

They may be obtained as follows :--

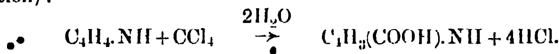
1. *Methods similar to the preparation of phenol acids* :—

(*a*) By the action of CO_2 on potassium pyrrols :



$$C_4H_4.NK + CO_2 \rightarrow C_4H_3(COOK).NH.$$

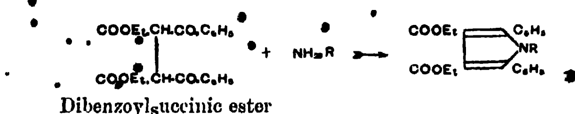
(*b*) By the action of CCl_4 upon pyrrol in presence of alkalies (Reimer's reaction) :



$$C_4H_4.NH + CCl_4 \xrightarrow{2H_2O} C_4H_3(COOH).NH + 4HCl.$$

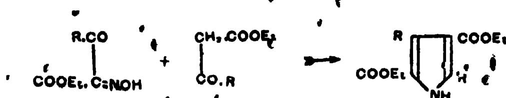
2. *Other methods* :—

(*a*) Action of alcoholic amines on γ-diketocarboxylic esters :



Dibenzoylsuccinic ester

(*b*) Reduction of a mixture of a β-ketonic ester and its isonitroso-compound:

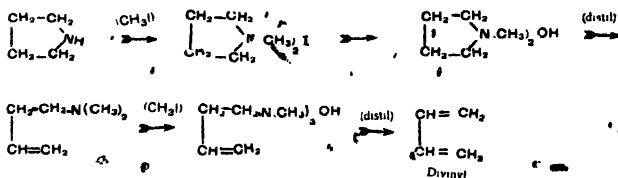


By gentle reduction of pyrrol (zinc-dust in acetic acid) a dihydropyrrol, *pyrroline*, is formed, and on more energetic reduction (phosphorus and hydriodic acid) the remaining double bond is eliminated and tetramethyleneimide or *pyrrolidine* results. Both reduction products are strong bases. Pyrrolidine is also formed by heating *putrescine hydrochloride*, $NH_3Cl[CH_2]_4.NH_2.HCl$ (formed by reduction of succinonitrile), and by reducing *succinimide* with sodium in alcohol (cf. *pyrrol*, p. 52).

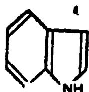
It affords another interesting case of relative ring-stability, since *piperidine* on methylation furnishes a quaternary ammonium hydroxide which readily rearranges to a derivative of methylpyrrolidine:



Pyrrolidine itself is finally converted to an unsaturated hydrocarbon, *divinyl*, when submitted to exhaustive methylation:



Substances like *butyrolactam* or *succinimide* are of course derived from ketopyrrolidine.

Benzopyrrol or *indol*, , is an important compound

which is frequently found in decaying albumen, and which is, moreover, very closely related to the important dye-stuff *indigo.*

It is obtained:

(*a*) Pyrogenetically, by heating many alkylanilines (*e.g.* cumidine, $C_6H_2(CH_3)_3NH_2$) to redness in glass tubes; by distilling indigo and its derivatives with zinc dust; and by fusing albumens with potash.

(*b*) From *o*-aminochlorostyrolene, $C_6H_4<{CH{=}CHCl \atop NH_2}$, by elimination of HCl.

(*c*) By reduction of *o*-nitrocinnamic acid.

It is a solid with a characteristic smell, closely resembling pyrrol in chemical behaviour.

General synthetic methods for the production of indols include:

(*a*) Ring-formation from *o*-aminoaromatic compounds:

$$C_6H_4<{CH_2.CO.R \atop NH_2} \longrightarrow C_6H_4<{CH \atop NH}>C.R$$

(*b*) The action of heat on phenylhydrazones in presence of HCl or $ZnCl_2$:

$$C_6H_5.NH.N{:}C<{R \atop CH_2.R'} \longrightarrow C_6H_4<{CR' \atop NH}>CR + NH_3$$

In this reaction *pyrazoles* (p. 66) are also frequently produced.

There are three possible modes of alkyl substitution of the indol nucleus:

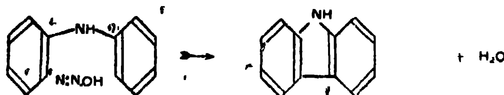
N-alkylindols (NR) — α-alkyl indols (NH, R at α) — β-alkyl indols (NH, R at β)

The most important alkyl derivative is *skatole* (β-methyl indol), which occurs with indol in mammalian fæces. The indol carboxylic acids are obtained by exactly similar methods to those used in the preparation of the pyrrol acids; the remaining important indol compounds owe their interest to their connexion with indigo, and will be discussed in the next section.

Dibenzopyrrol, [structure with NH], or *carbazole*, as it is usually called,

is found in the anthracene fraction of the products of coal-tar distillation, and is extracted therefrom commercially by fusion with potash, when the potassium derivative (as usually happens in the pyrrol series) is formed. It is a very feeble base, and is of some technical value as the source of several dyes. It may be synthesized :—

(*a*) By leading diphenylamine through red-hot tubes.
(*b*) By heating thiodiphenylamine with copper powder.
(*c*) By warming the diazo-derivative of *o*-aminodiphenylamine :



V.—INDIGO.

By far the most important member of the group of compounds now being described is the dye-stuff *indigo*, which is found in certain plants (notably in *indigofera anil* and in woad, *isatis tinctoria*) in the form of a glucoside *indican*. When the plants are submitted to the action of a specific ferment present (*indimulsin*) by crushing them with water in basins exposed to the air, the glucoside is decomposed and *indigo-blue*, together with some inferior colouring matters whose nature has only recently become fully understood, is precipitated. It is best purified by reduction with alkaline glucose solutions or with calcium hyposulphite, when the dye is converted to colourless soluble *indigo-white*, the by-products being mainly insoluble. The filtered solution is left exposed to the air, and indigo-blue is then reprecipitated.

Although indigo has been used both by civilized and savage races since a remote period, no ideas of its real nature existed until within the past eighty years. Indeed, up to the close of the phlogistic period of chemical history, it was usually regarded as a "mineral." Its empirical composition (C_8H_5ON) was established about 1830-1840, and soon afterwards Fritzsch distilled

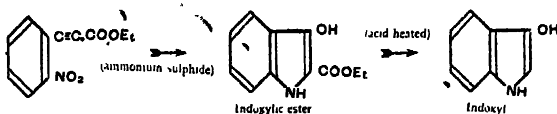
it with caustic potash and obtained an oil, identical with "cyanol" from coal-tar or from the reduction of nitrobenzene, to which he gave the name *aniline*. Somewhat later the oxidation product from indigo with nitric acid, $C_8H_5O_2N$, was characterized and designated *isatin*. There matters remained until Baeyer commenced the systematic investigation of the decomposition-products of indigo about 1865, and having elucidated its structure, proceeded to devise synthetic methods for its production (1880-1890).

The broad outlines of Baeyer's work are as follows:—

(1) He reduced indigo successively to indoxyl and indol.

(*a*) As we have already seen, he synthetically proved *indol* to be benzo-pyrrol: indigo was transformed to indol by heating with zinc-dust.

(*b*) Indoxyl, C_8H_7ON, was obtained by fusing indigo with caustic potash in absence of air, as an unstable oil. Since it yielded a nitroso-compound, it evidently contained an imino-group, and was consequently regarded as an oxy-indol. This view was confirmed by Baeyer's synthesis from *o*-nitrophenylpropiolic ester:

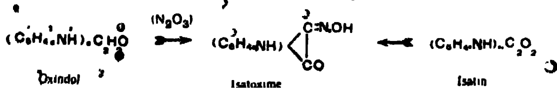


The indoxylic ester first formed yields the acid on saponification, and this loses CO_2 on heating.

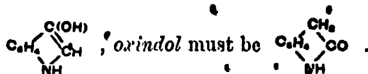
(2) He next examined the oxidation-product *isatin*, $C_8H_5O_2N$, from which by reduction with zinc-dust and acid he obtained *dioxindol*, $C_8H_7O_2N$, which by further reduction with sodium amalgam gave *oxindol*, C_8H_7ON.

(*a*) *Oxindol* readily reoxidizes to *dioxindol*, and the latter substance to isatin.

(*b*) With nitrous anhydride, *oxindol* yields an *iso-nitroso-compound* identical with an *oxime* obtainable from *isatin*. Consequently, assuming the indol nucleus present throughout, we have :

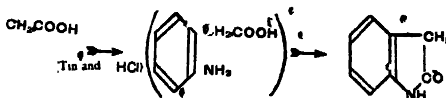


Therefore it is probable that *isatin* is $C_6H_4\langle{}^{CO}_{NH}\rangle CO$, and since *indoxyl* is

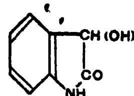


, *oxindol* must be .

(*c*) This was established independently by the synthesis of oxindol from *o*-nitrophenylacetic acid:



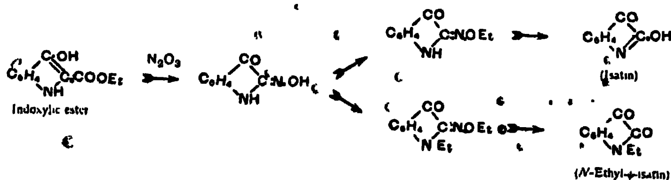
(*d*) *Dioxindol* was next shown to be



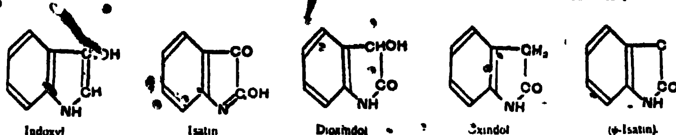
(3) Baeyer found that *isatin*, although apparently possessing two carbonyl groups, yielded only a monoxime (*isatoxime*), whilst by the action of PCl_5 upon isatin a chloro-derivative was produced, indicative of the presence of a hydroxylic group. He therefore suggested that isatin was $C_6H_4\langle{}^{CO}_{N}\rangle C.OH$, and this was borne out by the following facts:—

(*a*) *Isatoxime* (which becomes $C_6H_4\langle{}^{C:N.OH}_{N}\rangle C.OH$), yields, with ethyl iodide, a *mono-* and a *di-ethyl ether*, both of which revert to *isatin* on hydrolysis.

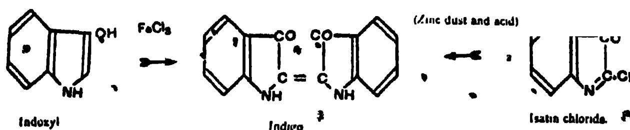
(*b*) Nitrous acid reacts with *indoxylic ester* (see above), forming an *isomeric* isatoxime (*ψ-isatoxime*); this also furnishes *mono-* and *di-ethyl ethers*, but here only the mono-ethyl ether reverts to isatin:



The structure of these derivatives was now established:



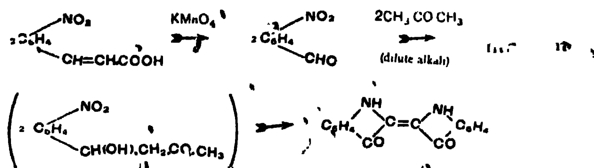
and that of *indigo* itself followed, since the dyestuff resulted from simple oxidation of *indoxyl* or from reduction of *isatin chloride*:



The determination of the vapour density of indigo agreed with this formula.

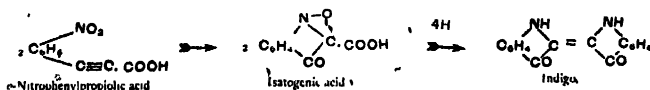
It remains to describe the complete syntheses of indigo effected by Baeyer, starting from *o*-nitrocinnamic acid:—

(*a*) By oxidation of this substance *o*-nitrobenzaldehyde was prepared; this condenses in the usual manner with acetone to an "aldol" derivative which can be hydrolysed by alkalies, when one of the products of saponification is indigo-blue:

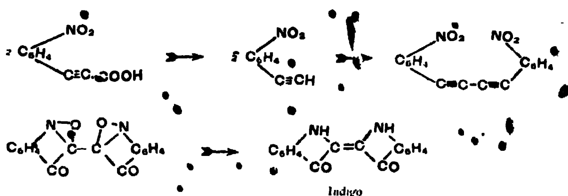


(*b*) *o*-Nitrophenylpropiolic acid is obtained from *o*-nitrodibromcinnamic acid, and then either—

(i) Directly reduced to indigo by a mild alkaline re-agent:



or (ii) Converted to *o*-dinitrodiphenyldiacetylene through *o*-nitrophenylacetylene, the latter compound then being reduced:



Various commercial processes for synthesizing indigo have also been devised, but until recently none of these were remarkably successful.

The earliest suggestions in this direction were for the fusion of compounds, such as ω-bromacetanilide or ethylene anthranilic acid, with caustic alkali; a more promising starting material has been found in *phenylglycocoll*, or better, its *o*-carboxylic acid, which is conveniently made from anthranilic and chloracetic acids. The product, $C_6H_4\langle{}^{COOH}_{NH.CH_2.COOH}$, is then submitted to potash fusion, when indoxyl is produced and rapidly converted to indigo by atmospheric oxygen. This method, known as Heumann's process, is not yet perfected, the latest procedures being to reduce the phenylglycocoll with magnesium powder in presence of a mixture of fused sodium, potassium and barium hydroxides, and to conduct the operation at 200-230° under reduced pressure. 80-90 per cent of indigo may then be obtained.

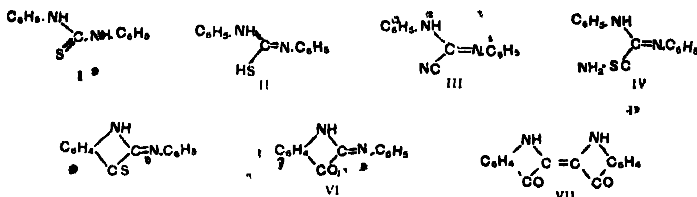
A still better procedure has been devised by Sandmeyer, starting from crude aniline and carbon disulphide. When heated together these form thiocarbanilide (I), which is boiled in an autoclave with water containing lead carbonate and potassium cyanide. The thiocarbanilide reacts in the tautomeric form (II), and the mercaptyl group is replaced by the cyanide radicle (III). This product is reduced in the usual manner by ammonium sulphide, the corresponding thio-amide (IV) being formed. On heating the latter with strong sulphuric acid the following reactions occur:

(i) Condensation to an indol derivative (V).

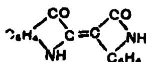
(ii) Replacement of the sulphur present by oxygen (VI).

(iii) Elimination of the anilido radicle with formation of indigo (VII).

(iv) Sulphonation of the indigo to the indigo-carmine acid (see below).

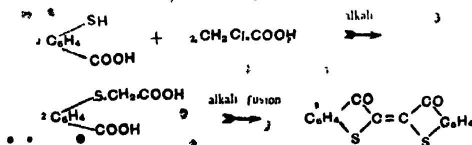


Mono- and di-sulphonic acids of indigo are frequently used in place of indigo itself, sodium indigotin-disulphonate being technically known as *indigo-carmine*; *indigo-red* and *indigo-brown* (*indirubin*) are two bodies isomeric with indigo and occurring with it in nature, but are not so valuable tinctorially as indigo itself. Indirubin has been proved to be



Very recently, the corresponding derivatives of benzothiophnee, $C_6H_4\langle^{CO}_{S}\rangle C=C\langle^{CO}_{S}\rangle C_6H_4$, have been synthesized, and under the names of thioindigo, thioindirubin, etc., are finding considerable technical application.

Thioindigo, which is deep red in colour, is prepared by alkaline condensation of thiosalicylic and chloracetic acids and subsequent alkaline fusion :—

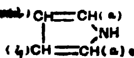


CHAPTER V

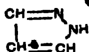
FIVE-MEMBERED POLYHETEROATOMIC RINGS: THE AZOLES (OR RING-SUBSTITUTED NITROGEN DERIVATIVES OF FURFURANE, THIOPHENE, AND PYRROL)

I. GENERAL

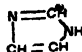
THE preceding chapter was concerned with the heterocyclic ring systems containing four carbon atoms and one other (oxygen, sulphur, or nitrogen) and we have now to consider the numerous series derivable from each of these by substituting one or more nitrogen atoms for one or more of the =CH- groups therein. Taking as our example the substituted pyrrol compounds (which are the most important), it is seen at once that there are two ways of replacing one methine group by nitrogen:



Pyrrol



Pyrro-(a)-monazole



Pyrro-(b)-monazole

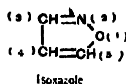
The number of isomeric ring-systems increases when two methine groups are replaced by nitrogen atoms, and a rational generic nomenclature becomes essential to ready comprehension of these various types. Unfortunately, but naturally, the different series of the group were not all worked out contemporaneously or on a settled plan, and so different group-names have been proposed from time to time. Richter has put forward a better system, starting from the general designation *azole* for any derivative of furfurane, thiophene, or pyrrol which possesses nitrogen in place of the ring =CH- groups. The number of such

nitrogen atoms introduced is suggested by the appropriate prefix *mon-*, *di-*, or *tri-*, and the nature of the original ring-system from which that in question is derived is shown by the further prefix *furo-*, *thio-*, or *pyrro-*. Finally, the methine groups of the pyrrol, etc., nuclei are termed *a*, a_1, *b*, b_1, as shown above, and a simple but obvious nomenclature results. Thus in the subjoined table will be found a list of all the types of compounds discussed in this chapter, in which the formulæ and generic name of the pyrrol compounds are used as typical of the rest, whilst in addition the common names of each corresponding system (oxygen, sulphur, and nitrogen) are given in successive columns:—

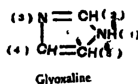
Formula	Name	*Furo-azoles*	*Thio-azoles*	*Pyrro-azoles*
CH=N, NH, CH=CH	Pyrro(a)monazole	Isoxazole	Isothiazole	Pyrazole
N=CH, NH, CH=CH	Pyrro(b)monazole	Oxazole	Thiazole	Glyoxaline or Imidazole
CH=N, NH, CH=N	Pyrro(aa_1)diazole	Azoxazoles	—	Osotriazole
CH=N, NH, N=CH	Pyrro(ab_1)diazole	Azoxime	Azosulphime	Triazole
N=N, NH, CH=CH	Pyrro(ab)diazole	Diazo-oxides	Diazosulphides	Azimides
N=CH, NH, N=CH	Pyrro(bb_1)diazole	Oxybiazole	Thiobiazole	Triazole
N=N, NH, CH=N	Pyrro(aa_1b)triazole			Tetrazole
N=CH, NH, N=N	Pyrro(abb_1)triazole			Tetrazole

The nomenclature of the external substituents in these various series has also been rather lacking in general system. Some indications of the different methods adopted may be given here: the simplest method is to number the atoms, beginning at the

original (furfurane, thiophene, or pyrrol), heterocyclic atom, proceeding in the direction of the nearest nitrogen ring-substituent:

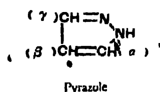


Isoxazole

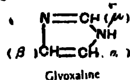


Glyoxaline

Frequently, however, in the case of (*a*)-*monazoles*, the carbon atoms are designated α, β, γ, commencing from the original heterocyclic member,



Pyrazole

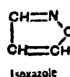


Glyoxaline

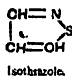
whilst the intermediate methine group in (*b*)-*monazoles* is called μ. In simple substitution products of the more complex diazole rings it is often sufficient merely to refer to the substituents as *C*- or *N*- alkyl derivatives, as the case may be.

II. Isoxazoles and Pyrazoles

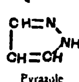
We will discuss, in the first place, the (*a*)-monoazosubstituents, which are also the most important in the whole group, and are derived from:



Isoxazole

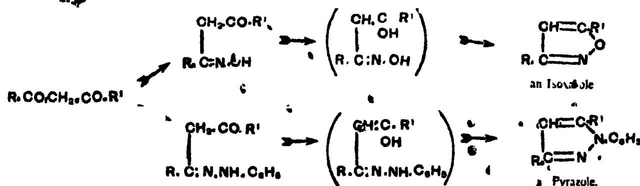


Isothiazole

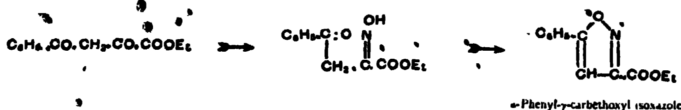


Pyrazole

Very few *isothiazole* compounds are known, but *isoxazoles* or *pyrazoles* may respectively be formed by dehydration of the monoximes or monophenylhydrazones of β-diketones:

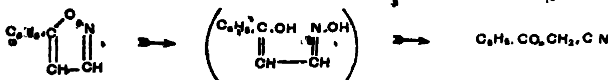


If the oximes or phenylhydrazones of β-di-ketonic esters are used, esters of the corresponding carboxylic acid derivatives are produced, from which the acids themselves may be isolated:

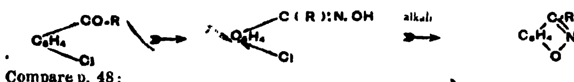


α-Phenyl-γ-carbethoxyl isoxazole

Isoxazole itself has not been prepared, but various alkylisoxazoles are known, and these are, as a rule, well characterized substances. Under certain circumstances, however, the ring-system may be rendered unstable; thus, if the γ-carbon atom is unsubstituted, whilst elsewhere in the ring there are acidic radicles, an open-chain ketonic cyanide may readily be formed:



Aromatic isoxazoles (*benzisoxazoles*) are also known, and have been synthesized from substituted *o*-halogen acetophenones:

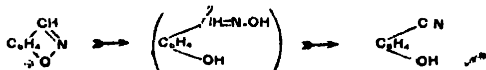


Compare p. 48:

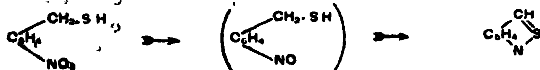


(Coumarone)

Here again the stability of the five-membered ring is influenced by the nature of the aromatic group; and accordingly the unsubstituted *benzisoxazole* (the parent member) does not exist, but at once rearranges to salicylicnitrile:



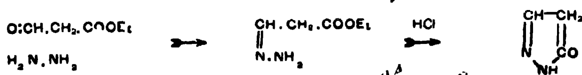
The corresponding *isothiazole* and its alkyl derivatives have not been isolated, but the first member of its aromatic series, *benzisothiazole*, is an oil formed by reducing *o*-nitrobenzylmercaptan:



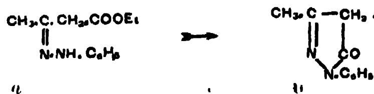
By far the most interesting members of the class we are now studying, however, are the *pyrazoles*, which have proved important both to organic theory and to the technical side of the science. Their systematic investigation was commenced by Knorr in 1883; the first part of his work dealt with derivatives of a reduced pyrazole (*pyrazoline*), $\begin{matrix} CH{=}N \\ | \quad\quad > NH \\ CH_2{-}CH_2 \end{matrix}$, of which the simplest was *pyrazolone*, $\begin{matrix} CH{=}N \\ | \quad\quad > NH \\ CH_2{-}CO \end{matrix}$.

It will be seen that the relationship of pyrazolone to pyrazole is similar to that of butyrolactone to furfurane (p. 47).

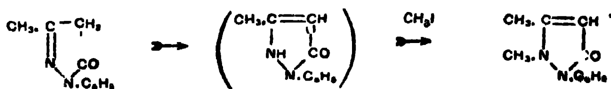
The simplest method of formation of pyrazolone is the condensation of hydrazine with formylacetic ester in presence of an acid-condensing agent:



Substituted pyrazolones are equally readily formed by acting on other β-ketonic esters with hydrazine or monoalkylhydrazines, and in this way Knorr prepared *N*-phenyl-3-methylpyrazolone from acetoacetic ester and phenylhydrazine:

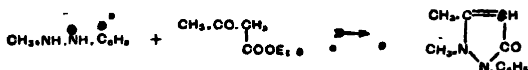


On treating this compound with methyl iodide at 100°, a methyl group is attached to the second nitrogen atom, an intramolecular rearrangement being presumed to take place:



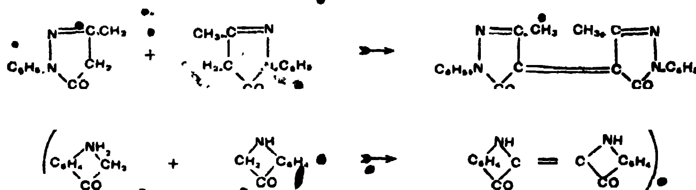
The new compound, 1-*phenyl*-2, 3-*dimethylpyrazolone*, is a basic substance with strong antipyretic properties, and has found

immense use in medicine under the name of *antipyrine*. Its structure has been confirmed by its synthesis from acetoacetic ester and symmetrical methylphenyl-hydrazine :



Returning to phenylmethylpyrazolone, whose chemical behaviour is typical of the other pyrazolones, it may be remarked that that substance is both feebly basic and acidic, in virtue respectively of the tertiary nitrogen atoms and of the group $=CH.CO-$. The presence of the latter group also leads to a number of condensation reactions with aldehydes, nitrous acid, etc., similar to those undergone by other ketones containing the system $-CH_2.CO-$, accompanied by other unsaturated radicles.

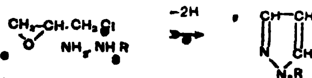
Again, phenylmethylpyrazolone is easily oxidized to a deep blue dye-stuff very similar to indigo-blue (*pyrazole blue*) :



When *pyrazolones* are distilled with zinc dust, the corresponding pyrazoles are formed ; the pyrazoles themselves are also produced in the following reactions :—

(*a*) Condensation of mono-hydrazones or mono-alkylhydrazones of β-diketones (pp. 17, 65).

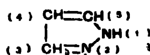
(*b*) Condensation of hydrazines with epichlorohydrin by means of zinc chloride, oxidation taking place at the same time :



(*c*) The action of heat on *pyrazole carboxylic acids.*

The latter compounds are formed by condensation of β-ketonic ester hydrazones, and also by the combination of diazomethane or diazoacetic ester with unsaturated dicarboxylic esters (p. 23).

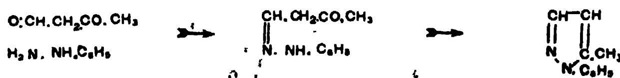
Pyrazole itself is a weak base, melting at 70°. It forms certain metallic derivatives in consequence of the presence of an imino group surrounded by unsaturated (negative) radicles:



Strictly speaking, however, this structural formula for pyrazole fails (in much the same way as the ordinary benzene formula) to express all the known facts. For it is obvious that the carbon atoms are in relatively different positions with respect to the atoms –N– and –NH–, whilst it has been found in practice that 3- and 5-substituted pyrazoles are identical. Thus Knorr synthesized 1-*phenyl*-3-*methyl* and 1-*phenyl*-5-*methyl-pyrazoles* as follows:—

1-*Phenyl*-3-*methylpyrazole*, m.p. 37°, by reduction of phenylmethylpyrazolone (p. 66).

1-*Phenyl*-5-*methylpyrazole*, b.p. 255°, from oxymethyleneacetone and phenylhydrazine:



The *N*-phenyl group was then split off by oxidation, and in each case the same *methylpyrazole* was obtained. Consequently it is supposed that the grouping =N–NH– exhibits tautomerism, the hydrogen oscillating between the two nitrogen atoms.

Other alkyl *pyrazoles* of this kind have been prepared from hydraine and various β-diketones, whilst *N-alkyl pyrazoles* have been obtained, either by means of the action of alkyl iodides upon pyrazole silver (the analogue of potassium pyrrol) or by condensing β-diketones with alkyl-hydrazines. Pyrazoles can be halogenated, nitrated, or sulphonated as readily as benzene, and

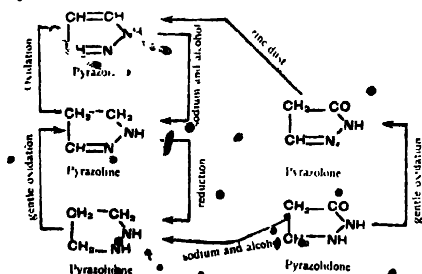
the substituted products undergo the same general reactions as the corresponding aromatic derivatives.

On reduction with sodium in alcohol, *pyrazolines* (dihydropyrazoles) are formed; these readily reoxidize to pyrazoles, or may be further reduced to tetrahydropyrazoles or *pyrazolidines*, which are still more susceptible to oxidation. These respective stages correspond to the pyrrols, pyrrolines, and pyrrolidines (p. 53).

The keto-derivatives of the *pyrazolidines* are obtained when β-bromoaliphatic acids react with hydrazine:

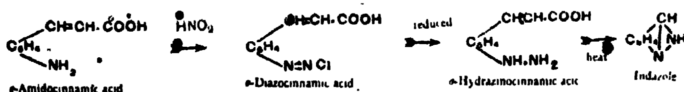


These *pyrazolidones* readily oxidize to pyrazolones. Consequently we may tabulate the reduction-products of pyrazole as follows:—

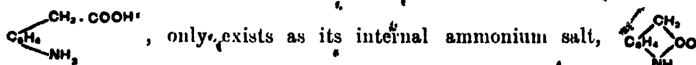


The condensed aromatic-pyrazole derivatives (*benzopyrazoles* or *indazoles*, corresponding to the indols in the pyrrol series) are not so important as the pyrazoles themselves. They may be obtained as follows:—

(*a*) By heating *o*-hydrazinocinnamic acids:

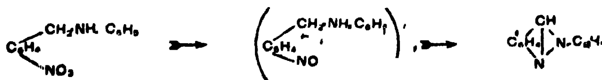


(It will be remembered (p. 57) that *o*-aminophenylacetic acid,

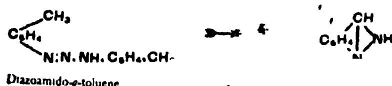


(oxindol); in the present case, however, the reaction involves the loss of a molecule of acetic acid, rather than the formation of the unstable seven-membered ring which cyclic ammonium salt-formation requires.)

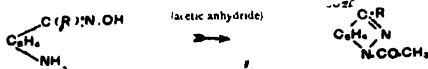
(*b*) By reduction of *o*-nitrobenzylaniline:



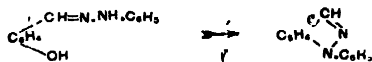
(*c*) From *o*-diazotoluene derivatives:



If, however, *o*-aminoketoximes are digested with acetic anhydride, we also get indazole derivatives, but different from those above in that the nitrogen atom adjacent to the benzene nucleus must now be substituted:



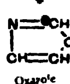
Similarly, a *phenylindazole* isomeric with that produced above by reducing *o*-nitrobenzylaniline is formed by condensing salicylaldehyde phenylhydrazone:—



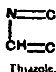
Consequently these latter compounds, mistermed "*isindazoles*," possess the real benzopyrazole structure, C_6H_4 CH N N, whilst the so-called *indazoles* must be formulated as above: C_6H_4 CH NH N. Both classes of substances are feeble bases, usually crystalline.

III. Oxazoles, Thiazoles, and Imidazoles (Glyoxalines)

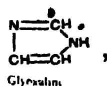
Of the three series of (b)-monazoles,



Oxazole



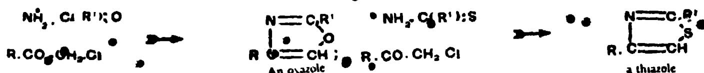
Thiazole, and



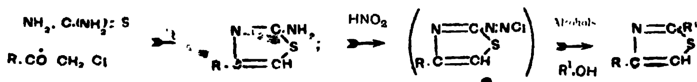
Glyoxaline,

the last are the most important, and we may briefly deal with the first two at the same time, since their general synthetic methods of production are parallel:

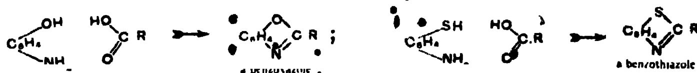
(1) From ω-chloroacetones and amides or thioamides:



Oxazoles are also formed by condensing benzoin with acid nitriles in presence of strong sulphuric acid, whilst thiazoles result from the decomposition of μ-aminothiazole (which may be produced from thiourea as above):



The corresponding *benzo*-derivatives are readily prepared by heating *o*-aminophenols or *o*-aminothiophenols with carboxylic acids:



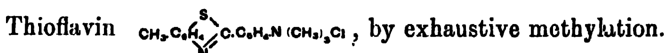
All these substances are feebly basic, crystalline compounds, not quite so stable as the average heterocyclic ring-compound (hot mineral acids, for example, break them up); they give rise to the usual series of substituted derivatives, none of which have any especial interest with the exception of a few dyes derived from the *benzo*-series in each case.

Thus, certain aminophenyl derivatives of benzoxazole, when diazotized and coupled with naphthol, give pink or red substan-

tive cotton dyes, whilst from *p*-*p*-aminophenyltoluthiazole,



(obtained commercially as "*dehydrothiotoluidine*" by heating thio-*p*-toluidine * with sulphur), the important yellow dyes *thioflavin* and *primulin* are manufactured as follows :—



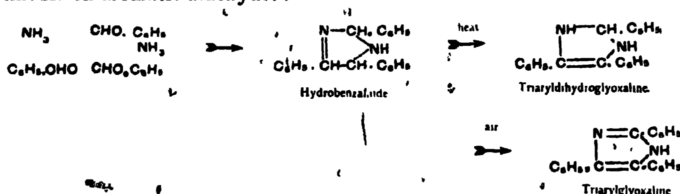
thio-*p*-toluidine and sulphur.

Glyoxaline was discovered by Debus in 1858, and received its name from its production from ammonia and glyoxal. Much later, general methods of synthesis were derived, and a more definite knowledge of the nature of the compound and its allied derivatives was obtained. The chief synthetic methods for the preparation of glyoxalines or imidazoles are :

(*a*) Condensation of *a*-diketones and aldehydes with ammonia :



(*b*) The action of heat on "hydrobenzamides," formed by the action of ammonia on aromatic aldehydes :

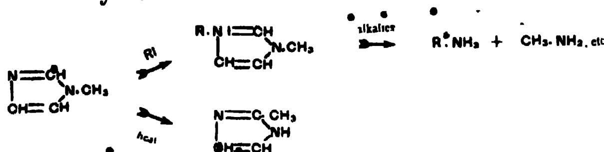


The glyoxalines are well-defined bases, but the imino-group is still sufficiently acidic to yield a silver salt, and to form *N*-alkylglyoxalines with alkyl iodides. These *N*-alkylglyoxalines readily

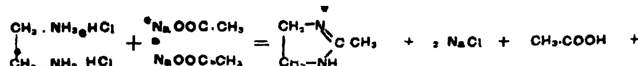
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* Diaminoditolyl sulphide $(NH_2(CH_3).C_6H_3)_2S$, formed by heating *p*-toluidine and sulphur with lead oxide.

add on another molecule of alkyl iodide to the second nitrogen atom, and the product is completely broken down by alkalies into a mixture of primary amines, formaldehyde, etc. On the other hand, the *N*-alkyl glyoxalines are isomerized to *μ*-alkyl derivatives by heat:

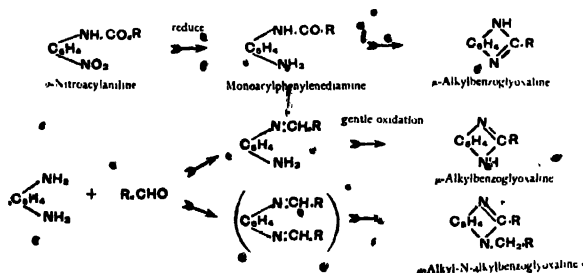


The glyoxalines, unlike pyrazole, cannot be reduced to hydro-derivatives, but the latter compounds may be prepared in other ways, notably by heating diacylethylenediamines (usually a mixture of ethylenediamine hydrochloride, and the sodium salt of an acid is heated instead of isolating the diacylcompound); thus:



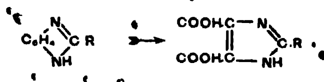
This particular compound, *μ*-methylglyoxalidine or *lysidine* is frequently prescribed for gout.

Benzoglyoxalines are formed in very similar fashion to the simple imidazole compounds from acylphenylenediamines as shown below.

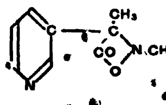


These compounds are less basic and more acidic than the alkyl glyoxalines, and are frequently soluble in cold aqueous

alkalies; by oxidation with potassium permanganate they yield *glyoxaline dicarboxylic acids*:—



A somewhat important alkaloid, *pilocarpine*, which occurs in Jaborandi leaves, and is a poison similar to nicotine in physiological effect, is a glyoxaline derivative, although formerly it was held to be a pyridine betaine of the structure:

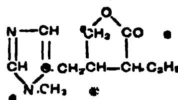


Pinner and Jowett showed, however, that it formed a methiodide which, by the action of alkalies, gave a mixture of aliphatic amines; moreover, when pilocarpine is distilled with lime, an alkyl glyoxaline is produced. On the other hand, it was found to give the characteristic reactions of a lactone, and upon oxidation with potassium permanganate gave a paraconic acid (which must contain the systems $\underset{\text{CO—O}}{-\text{C–C–C}}.\text{COOH}$ or $\text{COOH}.\underset{\text{CO—O}}{\text{C–C–C–}}$),

whilst potash fusion yielded ethyltricarballylic acid,

$$\begin{array}{r}CH_2.COOH\\ CH.COOH\\ C_2H_5.CH.COOH\end{array}.$$

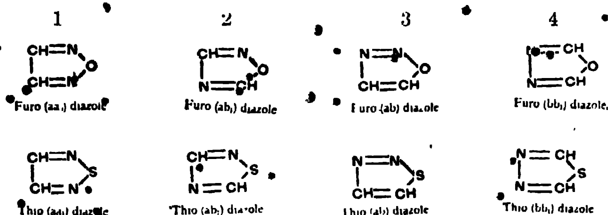
Summarizing all these facts, and remembering its dual nature of lactone and glyoxaline derivative, pilocarpine appears to be:



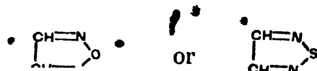
It is important to remember that *uric acid* and the *purines* are also glyoxaline derivatives, but as these also partake of the nature of pyrimidines, they will be discussed after the latter compounds have been described.

IV. Furo- and Thio-Diazoles

Having now completed the description of the more important monazole derivatives, in which one methine (=CH–) group of the furfurane, thiophene, or pyrrol ring is replaced by nitrogen (=N–), we must proceed to classify the numerous derivatives which, though of no great intrinsic interest, have been referred to systems in which two (and, in the next sections, three and four) of the =CH– groups are replaced by =N–. We have thus to consider four possible isomeric series of diazoles:



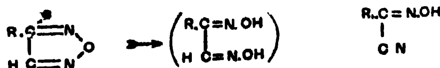
None of the parent members of this group are yet known, but a number of heterocyclic substances obtained by various reactions belong to one or other of the above four types.



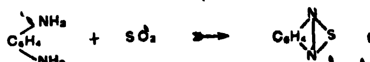
Dioximes of *α*-diketones yield ring compounds when boiled with alkalies which resemble the isoxazoles in chemical behaviour and have been called *azoxazoles*:



If one of the methine groups is unsubstituted a rearrangement to an acid nitrile readily occurs, as with the similar isoxazoles:

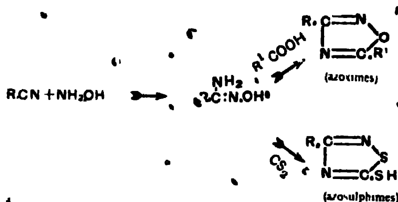


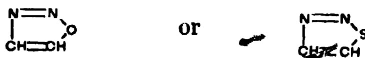
Only *benzo*-derivatives of *thio(ab)diazole* are known; these are formed from *o*-phenylenediamines and sulphur dioxide:



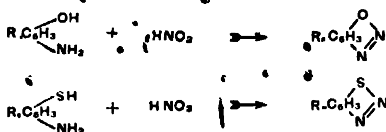
2. 

These result when amidoximes (from the addition of hydroxylamine to acid nitriles) are treated with carboxylic acids or carbon disulphide.

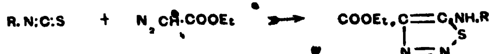


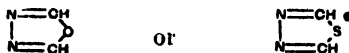
3. 

Practically only the *benzo*-compounds of this group are known; these are really cyclic diazo-oxides and sulphides, formed by diazotizing substituted aminophenols and thiophenols:

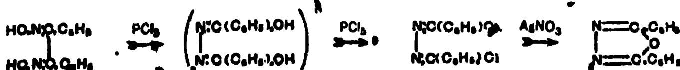


A few simple *thio(ab)diazoles* have also been prepared by the addition of diazomethane or diazoacetic ester to alkylisothiocyanates:

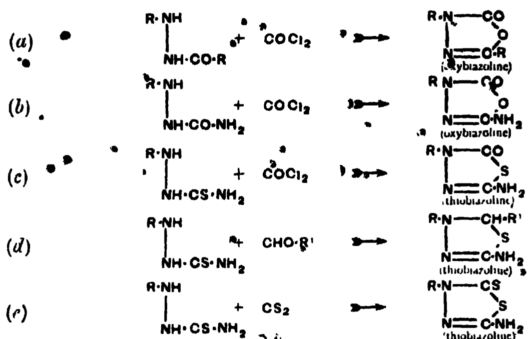


4. 

Derivatives of this group have also been obtained from α-diketonedioximes by the Beckmann rearrangement:

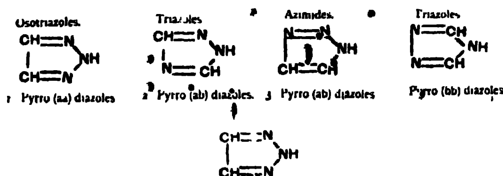


Keto derivatives of dihydrofuro- and thio-(bb_1)diazoles (*oxy* and *thio-biazolines*) are readily formed by condensation of aromatic hydrazines, semicarbazides, and thiosemicarbazides with carbonyl chloride, carbon disulphide, or aromatic aldehydes:



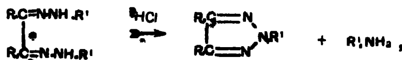
V. PYRRODIAZOLES (*so-called* TRIAZOLES)

Here again we have four different classes:—



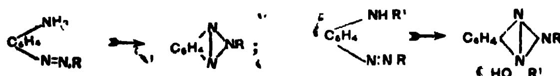
1.

The osotriazoles are produced when α-diketonediphenylhydrazones are heated with hydrochloric acid,



and are stable oils, feebly acidic in character.

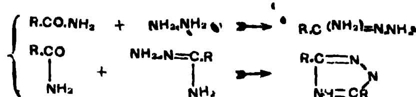
Their benz derivatives are formed when o-aminoazobenzenes are oxidized :



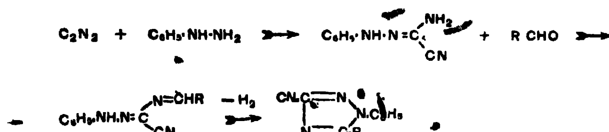
The four-membered heterocyclic compound *dimethylaziethane*, $CH_3C{=}N$ / $CH_3C{=}N$, from hydrazine and diacetyl, is an analogue of the osotriazoles.



Triazoles may be obtained by condensing hydrazine with excess of acid amides,



or by acting upon aldehydes or ketones with dicyanphenylhydrazine (from phenylhydrazine and cyanogen).

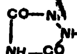


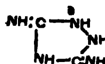
They are very weak bases, usually well-crystallized, and the imino hydrogen is replaceable by the alkali metals and silver. Numerous triazole derivatives are known, and it appears that the simple triazole molecule may alternate between



Thus *triazole* itself, a white crystalline body melting at 121°, and prepared from formamide and hydrazine, is supposed to be an equilibrium mixture of the two forms. On the other hand, when the iminohydrogen is replaced by alkyl groups, the two isomerides appear according to the particular methods of synthesis used.

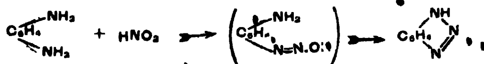
The *urazoles* are acidic derivatives of dihydrotriazole or *triazoline*, and are cyclic hydrazides of urea derivatives.

Thus we have *urazole*,  , from urea or biuret, and *guanazole*,

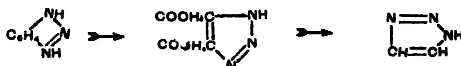
 , from dicyandiamide.



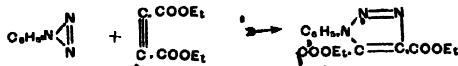
The *benzo*-derivatives of the *azimides* are formed when *o*-phenylenediamines are diazotized.



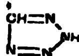
When these compounds, which can be distilled undecomposed, are oxidized by strong permanganate solutions, *pyrro(ab)diazole dicarboxylic acid* is formed, and on application of heat this leaves *pyrro(ab)diazole* or *azole*, the parent member of the group, which boils at 200°.



These compounds are also produced when diazobenzeneimide reacts with diethyl acetylenedicarboxylate:



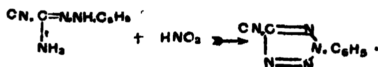
VI. Pyrrotriazoles (Tetrazoles)

This group of substances may be formulated either as 

or as , but in many cases, owing to lack of data and means of definitely synthesizing one or other form, it is not known to which system the tetrazoles really belong. They are,

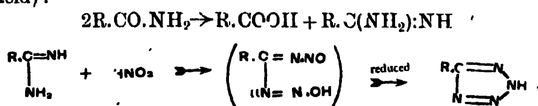
however, very interesting, because they involve the structural chemistry of nitrogen rather than of carbon, the ratio of nitrogen to carbon ring atoms being 4 : 1. They may be synthesized :

(*a*) From dicyanphenylhydrazine and nitrous acid :



(*b*) From nitrous acid and the amidines (from acid amides and hydrochloric acid) :

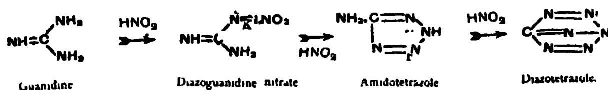
$$2R.CO.NH_2 \rightarrow R.COOH + R.C(NH_2):NH$$



This ring-system is almost as stable as that of pyrazole or triazole, and may be nitrated or sulphonated just like an aromatic hydrocarbon.

Its metallic imino-salts, however, are violently explosive, whilst certain derivatives of tetrazole still richer in nitrogen are amongst the most explosive substances known.

This guanidine, by the action of nitrous acid, yields diazoguanidine, which with more nitrous acid forms *aminotetrazole.* This is quite stable (m.p. 203°), but by further action of nitrous acid another diazocompound is produced, *diazotetrazole,* which explodes even in cold aqueous solution :



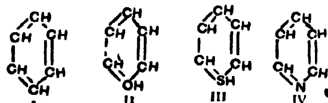
Guanidine — Diazoguanidine nitrate — Amidotetrazole — Diazotetrazole

CHAPTER VI

SIX-MEMBERED MONOHETEROCYCLIC RINGS: PYRONES, CHROMONES, AND XANTHONES, AND THEIR SULPHUR ANALOGUES

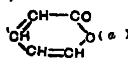
I. GENERAL

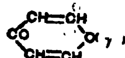
WE come now to the six-membered analogues of furfurane, thiophene, and pyrrol, which are also the monoheterocyclic compounds corresponding to benzene. Thus in the similar formulæ,



we see that I and IV represent the well-known classes of benzene and pyridine compounds respectively. We shall return to the study of pyridine and its derivatives in the next chapter; for the present we are concerned with the classes II and III. These, it may be said at once, do not exist as such; indeed, the only known members of the parent series II are the *xanthenes* (p. 90), $C_6H_4{<}^{O}_{CH_2}{>}C_6H_4$, and it is certain from analogy with *thioxanthene* (p. 97) that the substance is as here formulated, and not in the oxonium (II) form. Similarly, a few derivatives of the simple *penthiophene* series (III) have been prepared, but exist undoubtedly in the form $CH_2{<}^{CH=CH}_{CH=CH}{>}S$.

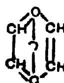
The most numerous and well-defined series are related, however, to oxy-derivatives of the simple ring-systems, and are known as *pyrones*,

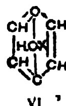


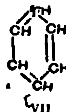
and


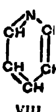
Benzo- and dibenzo-pyrones of each series are known, and these include many naturally occurring products of interest: they are reviewed in some detail in the succeeding pages, together with the corresponding sulphur analogues, when these are of sufficient importance.

We need only add at this point that the pyrones have been proved to contain oxygen in the quadrivalent state, whilst in the simple pyrones there is no evidence of a free carbonyl group. Consequently Collie has formulated the pyrones and their salts as (V) and (VI), and has also pointed out the analogy already referred to between the hypothetical reduced pyrones and pyridine, and has suggested the name *oxene* as a generic title for the parent compound (VII):



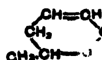






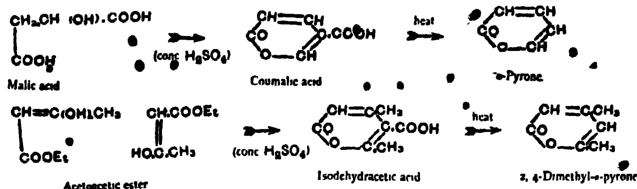
II. α-Pyrones

We have already met with reduced derivatives of α-pyrones under the heading of δ-lactones (for example, *δ-valerolactone* (*tetrahydro-α-pyrone*), $\overset{CH_2-CH_2}{CH_2}\!\!\!\diagup\!\!\underset{CH_2-O}{}\!\!\diagdown CO$, and *parasorbic acid* (*α-dihydro-α-pyrone*),

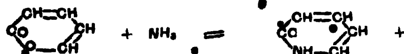


), and now proceed to describe the simplest α-pyrones, formed by heating their mono-carboxylic acids, which are in turn produced by the condensation of aliphatic oxyacids. The

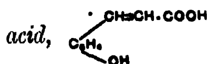
best known are *α-pyrone* itself (*coumalin*) and *dimethyl-α-pyrone*, obtained as follows:—



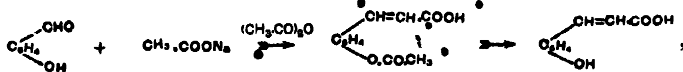
The α-pyrones are fairly readily broken down by alkalies, whilst with ammonia they at once yield lactams (α-pyridones; *cf.* pp. 8, 105):



The *benzo-α-pyrones* are important substances of the general structure, C_6H_4(CH=CH / O—CO), much used in artificial perfumery. The parent compound, *coumarin*, occurs in woodruff, melilot, and the Tonka bean, together with its corresponding oxy-acid, *o-coumaric acid*,



This acid has been synthesized by the Perkin reaction from salicylic aldehyde, sodium acetate, and acetic anhydride,

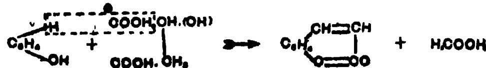


and by diazotizing *o*-aminocinnamic acid.

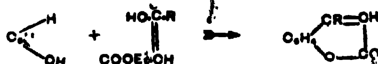
On boiling with acetic anhydride, or by heating the acetyl derivative first formed in the above reaction, *coumarin* is produced, but reverts to the acid on prolonged boiling with alkalies.

Two syntheses of coumarin derivatives are parallel to those of the simple α-pyrones:

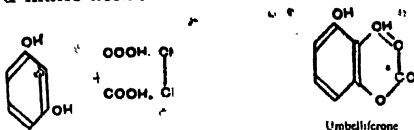
(*a*) From phenol and malic acid in presence of concentrated sulphuric acid:



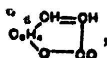
(*b*) From phenols and β-ketonic esters:



Various substituted coumarins have thus been prepared, and it has been found that the *oxy-coumarins* are in some cases identical with naturally occurring products. Thus *umbelliferone*, found in laurels and certain resins, has been synthesized from resorcinol and malic acid:



Umbelliferone

It will be remembered that the coumarin ring, 

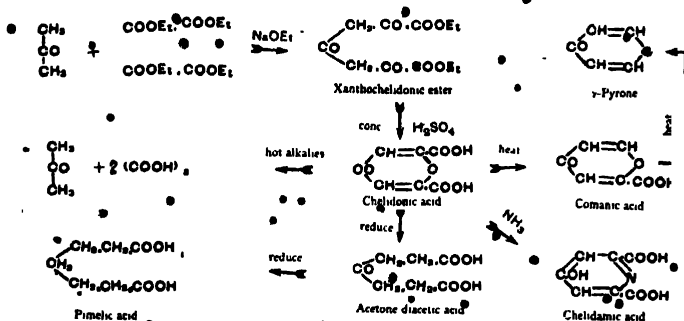
can be "degraded" into that of coumarone, C_6H_4 (CH, CH, O), that is, the six-membered pyrone system becomes a five-membered furfurane derivative (p. 48).

Isocoumarins of the type C_6H_4 (CH=CH, CO—O) are also known, but are not very important.

III. γ-Pyrones

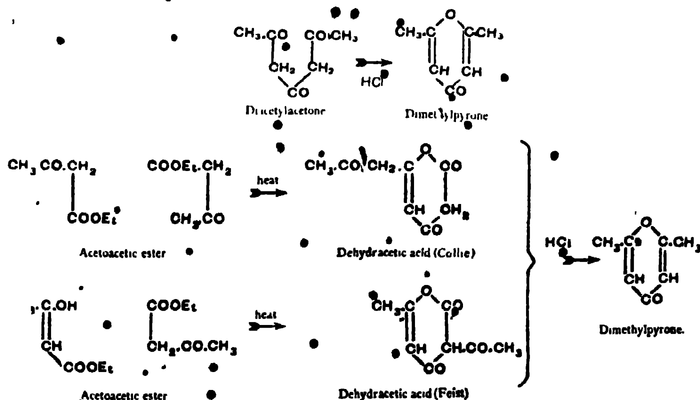
The parent members of this group are prepared, like the α-pyrones, by the action of heat on their carboxylic acids, when carbon dioxide is eliminated. A number of these acids occur in plants (notably *chelidonic acid* in celandine, and *meconic acid* in poppies). Chelidonic acid may be synthesized from acetone and diethyl oxalate, which condense to the ester of *acetone-dioxalic* or *xanthochelidonic acid* (the latter name suggested by the yellow colour of the salts of this acid), from which chelidonic acid (*pyrone αα¹-dicarboxylic acid*) results by the action of strong sulphuric acid. The latter acid is broken up by boiling aqueous

alkalies into acetone and oxalic acid, whilst on reduction it yields *acetonediacetic* and finally *pimelic acid*. Ammonia changes it to an *oxycarboxylic acid* of *pyridine*:



The structure of *meconic acid* follows from its similar conversion by ammonia to a pyridine derivative and its behaviour on treatment with hot alkalies.

An important alkyl-γ-pyrone is *dimethylpyrone*, which may be obtained from diacetylacetone by boiling with hydrochloric acid, or by similar treatment of *dehydracetic acid*, which is formed on boiling ethylacetoacetate, and which is formulated in either of the two ways shown below:

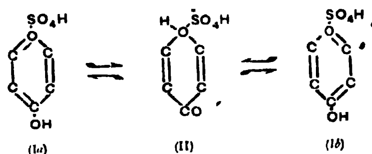


The typical reactions of the γ-pyrones are very interesting; as

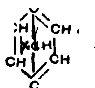
usual, cold alkalies resolve them into β-triketones, and hot alkalies break them up entirely into acetone and fatty acids, whilst ammonia replaces the oxygen by the imino-group to form γ-pyridones (γ-oxypyridines, p. 105). They all give deep colourations with alcoholic ferric chloride solution, whilst the carbonyl group in the simple γ-pyrones never yields oximes with hydroxylamine, although that in the dibenzo-γ-pyrones (xanthones) does.

This behaviour finds an exact parallel in the case of thiophene, the sulphur atom in which cannot be oxidized to a sulphone, whereas diphenylene-*o*-sulphide may be transformed to diphenylene-*o*-sulphone (p. 51).

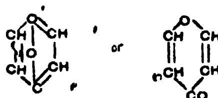
Again, all γ-pyrones give fluorescent solutions in strong sulphuric acid, a phenomenon which Hewitt has explained by the presence of double symmetric tautomerism in the salts which he assumes are formed:



On the other hand, Collie and Tickle have shown that the γ-pyrones are bases and yield well-defined mono-acid salts, to which they give the structure



the free pyrones being either



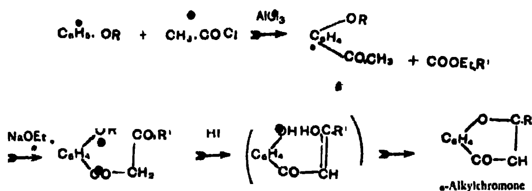
or an equilibrium mixture of both. This proof of the capacity of oxygen to form salts by virtue of its potential quadrivalent

condition is very important in view of other already known, but previously unexplained instances of a similar nature, notably the "molecular compounds" formed by ethers and acids or metallic salts; for example, $\frac{C_2H_5}{C_2H_5}>O<\frac{H}{Cl}$. Such cases are thus explained on the supposition that oxonium compounds are formed, thus bringing oxygen more into line with its analogue sulphur in the periodic system, and also accounting for the somewhat non-saturated nature of many oxygen compounds.

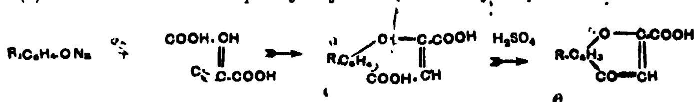
IV. Chromones and Xanthones (Benzo- and Dibenzo-γ-Pyrones)

Some important natural yellow and brown dyes are nearly related to the benzo-γ-pyrones; these will be enumerated in the next section, whilst in the present division we shall deal with the theoretically interesting members of these classes. The parent substances, corresponding to γ-pyrone, are usually known as *chromone*, , and *xanthone*, , respectively. Commencing with the first-mentioned compounds (the *monobenzo-γ-pyrones*), we may observe that syntheses of these have been effected along two general lines—(*a*) by Kostanecki; (*b*) by Ruhemann:

(*a*) The condensation of *o*-oxyacetophenones (from phenolethers and acetyl chloride by the Friedel-Crafts reaction, when a mixture of *o*- and *p*-alkoxy-acetophenones are produced, the latter (which are not here required) preponderating):



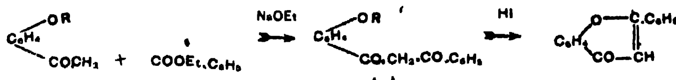
(*b*) The condensation of phenyloxyfumaric acids by sulphuric acid :



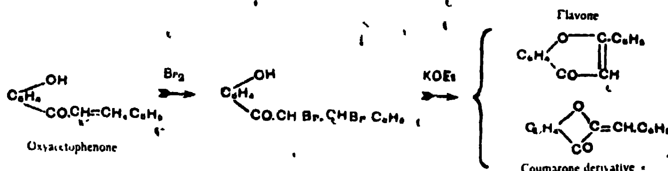
Chromone itself is obtained by heating the carboxylic acid from sodium phenate and chlorfumaric acid above its melting-point. All the simple chromones are colourless solids, dissolving to yellow or brown solutions in strong sulphuric acid, with fluorescence. They are resolved by alcoholic alkali into *o*-oxyacetophenones and formic acid.

The corresponding *chromene*, $C_6H_4\left<\begin{matrix}O-CH\\ \| \\ CH_2-CH\end{matrix}\right.$, is not known, but fully reduced *chromane*, $C_6H_4\left<\begin{matrix}O-CH_2\\ | \\ CH_2-CH_2\end{matrix}\right.$, results when γ-chloropropyl-*o*-aminobenzene is diazotized and boiled with alkalies.

The most notable chromone derivatives are the *α-phenyl-chromones* or *flavones*. It is the oxyderivatives of these which occur naturally as dyes. Flavones may be synthesized similarly to the chromones, using aromatic instead of aliphatic esters :

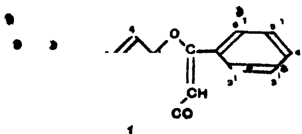


or they may be prepared from oxybenzalacetophenones, when coloured bye-products (coumarone derivatives) are usually encountered :

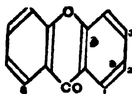


The *flavones* are distinctly acid in character, but at the same time they readily form oxonium salts ; alkalies decompose them in two ways, forming either oxyacetophenones and benzoic acid (compare the chromones above), or else salicylic acids and benzo-

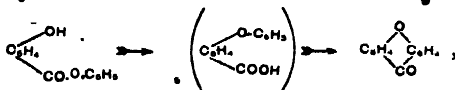
phenones. For convenient reference in connexion with the flavone dyes described a few pages later, it may be mentioned that substituted flavones are numbered as follows:



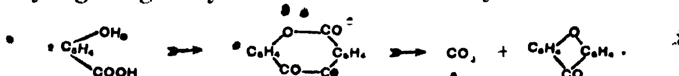
The *xanthones* or *dibenzo-γ-pyrones* resemble the anthraquinones in many ways and are derivatives of:



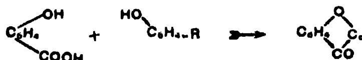
Xanthone, which is an almost colourless body yielding yellow and fluorescent solutions in sulphuric acid, is formed by heating salol (phenylsalicylate):



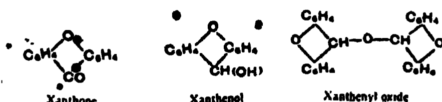
and by digesting salicyclic acid with acetic anhydride:



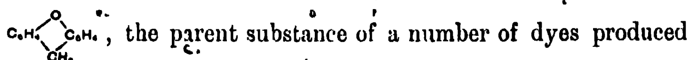
Similarly, salicyclic acid yields substituted xanthones when boiled with substituted phenols and acetic anhydride:



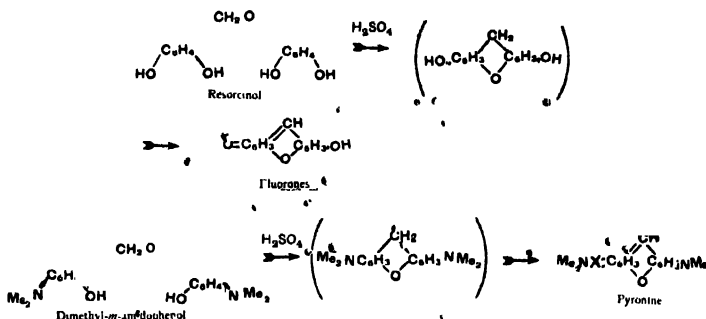
On reduction of xanthone, *xanthenol* is produced, a secondary alcohol which easily loses water and forms an oxide:



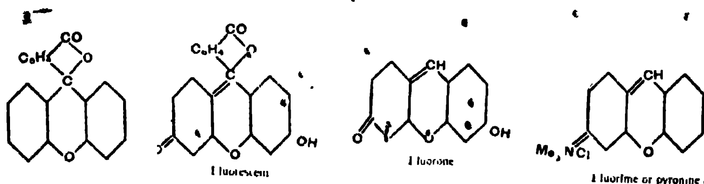
By more vigorous reduction, xanthone is converted to *xanthene*,



the parent substance of a number of dyes produced by the condensation of formaldehyde or methylene chloride with *m*-dioxy- or *m*-aminophenols:



The *pyronine* dyes were formerly much used; both series of compounds are pink fluorescent bodies, much resembling fluorescein (p. 33) in colour and chemical structure. Indeed, a convenient nomenclature for these derivatives has been based upon their relation to fluorane and fluorescein. Thus we have:



V. Naturally occurring Flavones and Xanthones

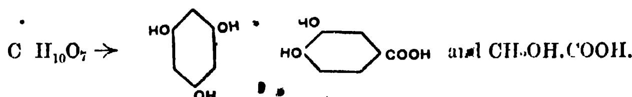
Many oxyderivatives of flavone and xanthone occur in the form of glucosides in the vegetable kingdom, and have been used as dyes for many years; their nature has, however, become known only recently, mainly owing to the researches of A. G.

Perkin, who attacked the problem from an analytical standpoint, and of Kostanecki, who has synthesized numerous members of the group.

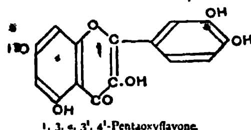
It will be sufficient to describe in some detail the means used to determine the constitution of one member of each class, since all the chemical methods are based on the same principle.

We will commence with *quercetin*, a yellow dye-stuff occurring in onions, oaks, and horse-chestnut buds, in the form of a glucoside *quercetrin*, and the most important natural dye-stuff known, with the exception of indigo and alizarin.

It was found to be of a phenolic nature, and on methylation gave a *tetramethyl* derivative which could still be acetylated, yielding a *monoacetyltetramethylquercetin*. This proved the presence of five free hydroxyl groups, and indicated that one of these was in the benzene nucleus adjacent to the carbonyl group of the pyrone ring, since hydroxyl in this position cannot usually be methylated. The next step was to examine the products of fusion with caustic potash; these were found to be phloroglucinol, protocatechuic acid, and glycollic acid:

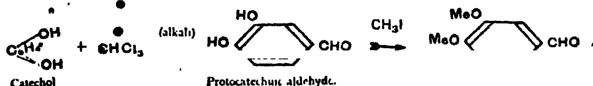


Remembering that there are five hydroxyl groups in quercetin, the following formula was then suggested:

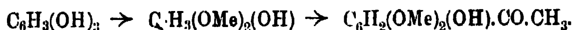


1, 3, 4, 3', 4'-Pentaoxyflavone.

This was confirmed later by a synthesis by Kostanecki, which proceeded from phloroglucinol and protocatechuic aldehyde. The latter compound may be synthesized from catechol by Reimer's reaction and then methylated:

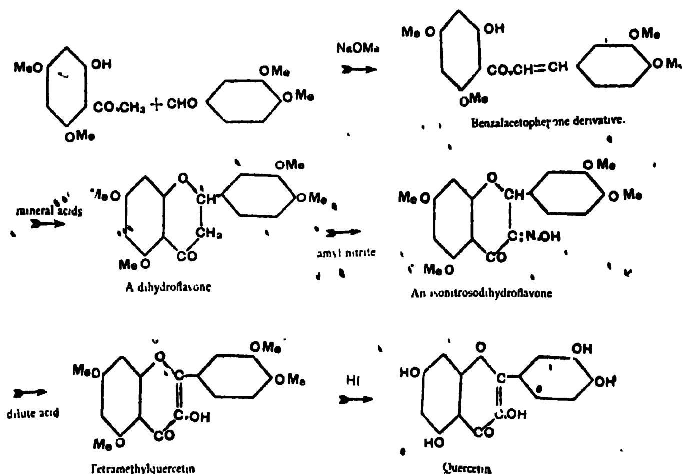


whilst the phloroglucinol is first converted to an acetophenone derivative :



$$C_6H_3(OH)_3 \rightarrow C_6H_3(OMe)_2(OH) \rightarrow C_6H_2(OMe)_2(OH).CO.CH_3.$$

These products are then united as follows :—

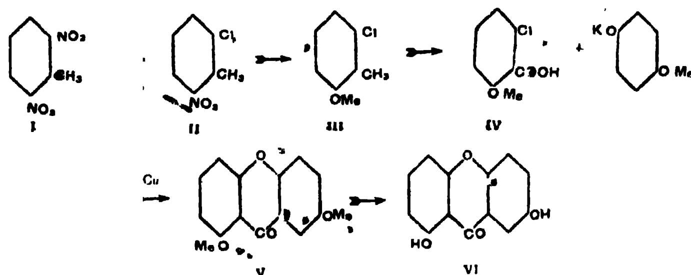


The following natural oxyflavones have thus been worked out and also synthesized :

		Source.	Products of potash fusion.	Position of OH groups.
Chrysin,	$C_{15}H_{10}O_4$	Poplar buds.	Phloroglucin, benzoic and acetic acids.	1.3.
Apigenine,	$C_{15}H_{10}O_5$	Parsley.	Phloroglucin, *p*-oxy-acetophenone.	1.3.4[1].
Luteoline,	$C_{15}H_{10}O$	Weld.	Phloroglucin, proto-catechuic and acetic acids.	1.3.3[1].4[1].
Fisetine,	$C_{15}H_{10}O_6$	Yellow cedar.	Resinous substances.	3.*a*.3[1].4[1].
Morine,	$C_{15}H_{10}O_7$	Yellow wood.	Phloroglucin, oxalic and β-resorcylic acids.	1.3.*a*.2[1].4[1]
Quercetin,	$C_{15}H_{10}O_7$	Oaks, chestnuts.	Phloroglucin, proto-catechuic and glycollic acids.	1.3.*a*.3[1].4[1].

The most interesting xanthone dye is *euxanthone* or *Indian yellow*, $C_{13}H_8O_4$, which occurs as the magnesium salt of *euxanthinic acid*. This acid, when hydrolysed with dilute mineral acids, gives euxanthone and *d*-glucuronic acid, CHO.[CH.OH]$_4$.COOH. The mode of extraction of the dye is somewhat quaint; it consists of feeding cows on mango leaves, and then evaporating their urine until a thick yellow precipitate of the magnesium salt separates. This primitive process is carried on in Bengal.

Euxanthone has been synthesized by Ullmann from 2.6-dinitrotoluene (I), which was converted successively into 2-nitro-6-chlorotoluene (II) and 2-methoxy-6-chloro-toluene (III), the latter compound being next oxidized to 2-methoxy-6-chlorobenzoic acid (IV). This was digested with the potassium salt of hydroquinone mono-methyl ether and copper powder when KCl was eliminated and the product finally condensed to a dimethoxyxanthone (V), which furnished 1.7. *dioxyxanthone*, identical with *euxanthone* (VI):



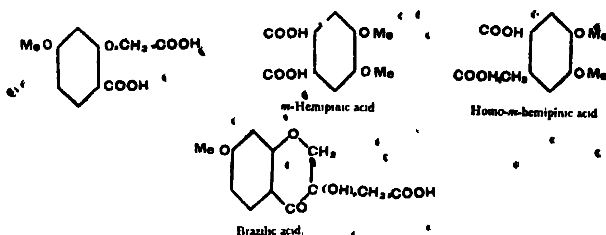
The chief xanthone dyes studied up to the present are enumerated below:

	Source.	Number of (CH_3O) Groups.	Position of Substituents. OH	OCH$_3$
Euxanthone, $C_{13}H_8O_4$	Mango leaves	—	1.7	—
Gentisine, $C_{14}H_{10}O_5$	Gentian	1	1.7	3
Datiscetine, $C_{15}H_{12}O_6$	Datisca	2	1.2	3.4

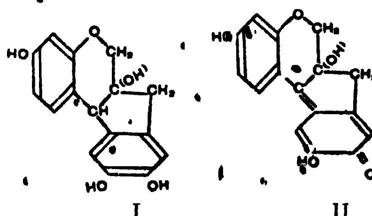
There remain two closely related colouring matters belonging to the flavone series, and occurring respectively in brazilwood and logwood. They are known as *brazilein* and *hæmatein*, and their constitutions have been unravelled by W. H. Perkin, jun., within the last few years. We cannot adequately describe here

all the experimental work involved, but it may be said that both brazilein, $C_{16}H_{12}O_5$, and hæmatein, $C_{16}H_{12}O_6$, pass easily by reduction into colourless *brazilin*, $C_{16}H_{14}O_5$, and *hæmatoxylin*, $C_{16}H_{14}O_6$, which by methylation yield *trimethylbrazilin* and *tetramethylhæmatoxylin*.

These products have been oxidized under various conditions, and the structure of most of the resulting oxidation-products has been synthetically proved. Thus trimethylbrazilin, treated, with potassium permanganate, gives the following four acids:



From a consideration of all the oxidation products of both alkylized derivatives, the following structures for *brazilin* (I) and *hæmatoxylin* have been built up; exit of hydrogen from these produces the quinonoid *brazilein* (II) and *hæmatein*:



Hæmatoxylin and hæmatein are almost identical with I and II respectively, but contain another hydroxyl group in the *benzo* part of the chromone ring, adjacent to the pyrone oxygen.

The Colour of the Flavone and Xanthone Dyes.

It will have been noticed that whilst the oxyderivatives of the ring-system, $<\begin{matrix}C=C\\C=C\end{matrix}>C{=}O$, are usually brilliantly coloured, the

pyrones themselves are colourless, although in strong sulphuric acid they give yellow and fluorescent solutions. It will also be remembered that the similar sudden appearance of colour in the phthaleins (p. 83) has been explained both on the basis of an ionic and a quinonoid theory. It is useful at this point, therefore, to devote a few words to the general theories of the nature of colour.

The oldest and most comprehensive hypothesis is really more of a classification of the facts than an attempt to explain them. It was first put forward by Witt in 1876, who showed that colour in organic compounds was frequently accompanied by a definite structure of part of the molecule.

Thus the nitro group, $-NO_2$, the azo group $-N=N-$, the *p*- and *o*-quinonoid nuclei, $=C\langle{C=C \atop C-C}\rangle C=$ and $\langle{C-C \atop C-C}\rangle$, are examples of groups which give rise to coloured compounds. Such systems were termed chromogens. It was realized later that many compounds, although chromogens, were not coloured, whilst others were coloured but were not dye-stuffs.

A *chromogen* was then defined as a molecular system in which the colour potentially due to a definite group (the *chromophore*) was developed by means of a salt-forming group (an *auxochrome*).

Thus, for example, we have:

	$C_6H_5NO_2$	NO_2	OH	$C_6H_4(OH)(NO_2)$
	Chromogen.	*Chromophore.*	*Auxochrome.*	*Coloured.*
or,	Flavone.	Pyrone ring.	OH	Oxyflavones.
	Chromogen.	*Chromophore.*	*Auxochrome.*	*Dyes.*

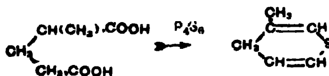
This classification has proved very useful, because it has appeared very plainly that most of the colour-producing groups contain several contiguous unsaturated atoms. This, taken in conjunction with the fact that "colour" is, after all, synonymous with the absorption by a molecule of light of a wave-length which can be appreciated by the human eye, leads to the idea that *absolute* (as distinct from physiological) colour (or selective

absorption of light) may be conditioned in some way by the nature of the unsaturation in a molecule.

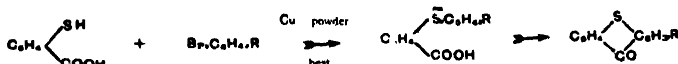
The alternative "quinonoid" theory of colour, which has been already mentioned (p. 33), leads to a similar conclusion, for Armstrong, in extending this view from the aromatic to the aliphatic series, assumed that unsaturated atoms, if present in sufficient numbers, can act as "light-absorbing centres," whose "co-operation" produces colour.

VI. Thio Derivatives of the Pyrones

But few derivatives of thio-α-pyrone or monobenzothio-α-pyrone are yet known, almost the only one being the so-called β-methylpenthiophene, $CH_2\langle{}^{C(CH_3)=CH}_{CH=CH}\rangle S$, which has been synthesized from α-methylglutaric acid and phosphorus sulphide, and is not very stable:



The *thioxanthones*, however, are a well-defined class, prepared by the action of strong sulphuric acid upon phenylthiosalicyclic acids:



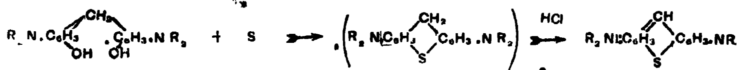
A better method has been recently devised by Smiles, who simply heats thiosalicyclic acid and an aromatic derivative with strong sulphuric acid.

This reaction undoubtedly depends on the primary oxidation of the thiosalicyclic acid to a sulphoxylic (R.S.OH) derivative, which then condenses:



Thioxanthone is reduced by alkaline reducing agents to *thioxanthenol*, $C_6H_4\left\langle {S \atop CH(OH)} \right\rangle C_6H_4$, which, like the xanthenols, readily yields an oxide, $S\left\langle {C_6H_4 \atop C_6H_4} \right\rangle CH{-}O{-}CH\left\langle {C_6H_4 \atop C_6H_4} \right\rangle S$; further reduction gives *thioxanthene*, $C_6H_4\left\langle {S \atop CH_2} \right\rangle C_6H_4$, which, unlike thiophene or thioxene derivatives, gives a sulphone, $C_6H_4\left\langle {SO_2 \atop CH_2} \right\rangle C_6H_4$, upon oxidation.

The important thiopyronine dyes, analogous to the fluorimes or pyronines, are related to thioxanthene, and are prepared commercially by digesting the condensation product of formaldehyde and dialkylamino-*m*-phenols with sulphur and lead oxide in water under pressure:

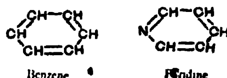


CHAPTER VII

SIX-MEMBERED MONOHETEROCYCLIC RINGS: PYRIDINES, QUINOLINES, ACRIDINES, AND THEIR REDUCED ANALOGUES

I. GENERAL

PYRIDINE and its derivatives are probably the most important of all heterocyclic compounds, and this for several reasons. From a general point of view, so many valuable drugs belong to this series, so many important dyes are derived from its benzo-derivatives (especially from the *acridine* group), and so many naturally occurring basic principles contain this ring-system as the basis of their generally very complex molecular structure, that it deserves considerable attention. On the other hand, from a chemical standpoint, although thiophene derivatives show a more striking correspondence with purely aromatic compounds in their physical properties, and the members of the furfurane series a closer chemical resemblance to the corresponding benzenes in chemical behaviour, yet *pyridine* is, of all of the heterocyclic series, the most nearly related to *benzene*, being derived therefrom simply by replacing a methine group by nitrogen:



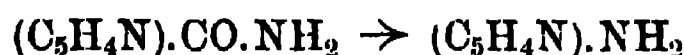
And when due allowance is made for the fact that the presence of a tertiary nitrogen atom must, by its basic properties, alter the fundamental character of the ring-system, it will appear that the pyridine series is quite as similar to the purely aromatic compounds as, for example, is the furfurane group.

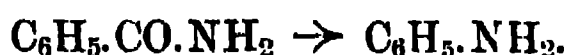
In support of this statement we may choose the following typical reactions:—

(*a*) Alkyl pyridines are oxidized by potassium permanganate to pyridine carboxylic acids:



(*b*) Aminopyridines can be obtained from the amides of pyridine acids by treatment with bromine and caustic potash:





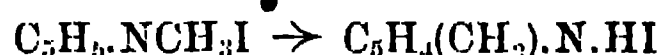
(*c*) Aminopyridines, on treatment with nitrous acid and warming, give the corresponding oxypyridines, just as anilines give phenols.

On the other hand, other decompositions illustrate the close parallelism between pyridine and pyrrol:

(*a*) Pyridine is readily reduced to piperidine, just as pyrrol passes into pyrrolidine:

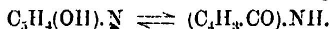


(*b*) *N*-alkylpyridinium halides can be rearranged by heat into α-alkylpyridines:



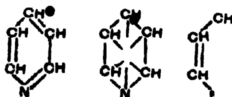


(*c*) Oxypyridines behave more like *lactams* than *phenols*, although reactions characteristic of both types of compound are shown by each oxypyridine:

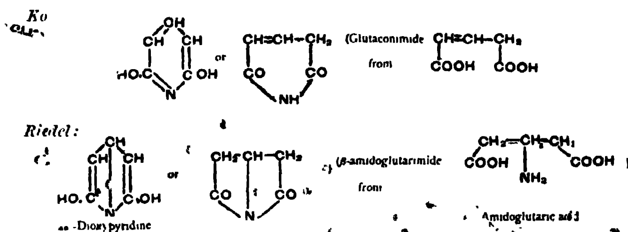


(*d*) Oxypyridines are convertible to chloropyridines by phosphorus chlorides.

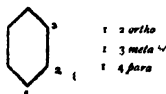
The structure of pyridine was discussed by Körner in 1869; following the lines of Kekulé's benzene theory, put forward two or three years earlier, he showed that pyridine could be represented excellently by formula I below. Much later Bamberger applied the Baeyer-Armstrong "centric" representation of benzene to pyridine, resulting in formula II. Either of these formulæ represent the transpositions of pyridine and its analogy to benzene.



A third formula, that of Riedel (III), differs from these in postulating a *para-* union between nitrogen and carbon; but, in addition to the fact that this formula does not correctly illustrate the equivalence of the hydrogen atoms in pyridine, it was shown by Kekulé that, for example, $\alpha\alpha^1$-dioxy-pyridine resembles more closely the imide of glutaconic acid than the imide of β-amidoglutaric acid (as would be necessitated by Riedel's formula). Consequently the choice of formulæ rests between I and II.



Either the Körner or the Bamberger formula accounts perfectly well for the position isomerism found in pyridine derivatives. The orientation of the different substituents was worked out by Körner between 1869 and 1877; we shall refer to the precise method, based upon the structure of the three pyridine monocarboxylic acids, when discussing the latter compounds. For the present it will suffice to point out the two methods in use for naming pyridine substituents, comparing these with the corresponding benzene position isomerides.



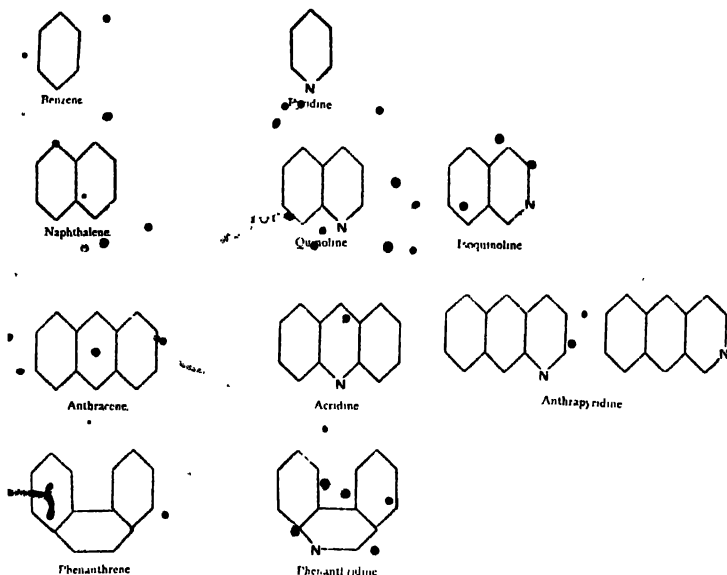


Just as the simplest alkyl benzenes (toluene, xylene, etc.) have received distinctive names, so the methyl, dimethyl, etc., pyridines are known by the following terms (the hexahydro-pyridines are similarly designated by inserting "*-pe-*" after the first syllable of the name):

Pyridine, C_5H_5N	*Methylpyridines*, C_5H_4MeN
Pyridine	Picolines
Piperidine	Pipecolines

Dimethylpyridines, $C_5H_3Me_2N$	*Trimethylpyridines*, $C_5H_2Me_3N$
{ Lutidines	Collidines
{ Lupetidines	Copellidines

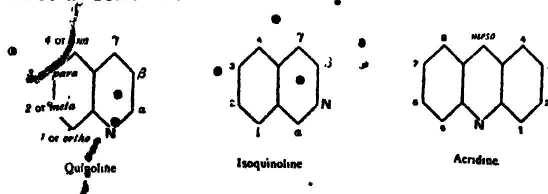
Finally, we may illustrate the correspondence between the condensed benzene and the benzopyridine, etc., series:



Benzene · Pyridine · Naphthalene · Quinoline · Isoquinoline · Anthracene · Acridine · Anthrapyridine · Phenanthrene · Phenanthridine

More complicated systems are also known, such as those derived from the annealing of a naphthalene with a quinoline, or a phenanthrene with an acridine nucleus.

The position-nomenclature generally used in the quinolines and acridines is as follows:



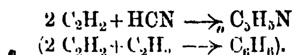
Quinoline · Isoquinoline · Acridine

II. Pyridine and its Derivatives

Pyridine and some of its simpler homologues are formed in the distillation of coal; a certain quantity of these substances always comes over during the manufacture of coal-gas, and is collected along with ammonia in the "gas-liquor," but the greater proportion remains in the coal tar, and is obtained in the distillation of the latter. Similarly, on distilling a variety of nitrogenous animal and vegetable products, members of this series are found in the distillate; they are present, for example, in marked quantity in bone-oil, whence they were first isolated by Anderson in 1846.

Various syntheses of pyridine and its derivatives have been effected at different times, mainly with a view to illustrating its relationship to the aliphatic series; the following half-dozen examples are the most interesting:

(*a*) On passing a mixture of acetylene and hydrogen cyanide through a red-hot tube, *pyridine* is formed in small amount (Ramsay) (compare the polymerization of acetylene alone to benzene):



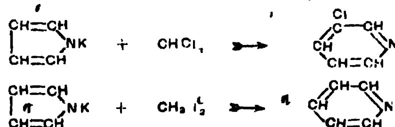
$$2\,C_2H_2 + HCN \longrightarrow C_5H_5N$$
$$(2\,C_2H_2 + C_2H_2 \longrightarrow C_6H_6).$$

(*b*) Piperidine and its derivatives (p. 120) are oxidized by concentrated sulphuric acid at 250-300° to the corresponding pyridines (Königs):

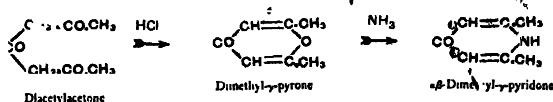


$$C_5H_{11}N \longrightarrow C_5H_5N + 6\,H.$$

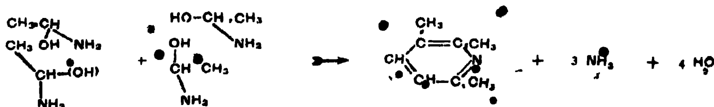
(*c*) Pyrrol potassium, when heated with aliphatic polyhalogen compounds, gives rise to pyridine derivatives:



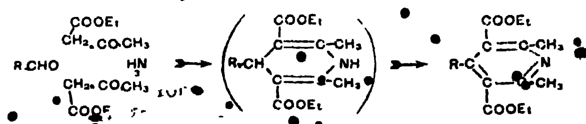
(*d*) Pyridones (p. 105) are produced by the action of ammonia upon α- γ-pyrones:



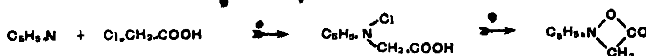
(*e*) Aldehyde ammonia compounds condense to pyridines when heated alone; for example:



(*f*) Pyridines are also formed by condensation of acetoacetic ester with aldehydes and ammonia (Hantzsch):

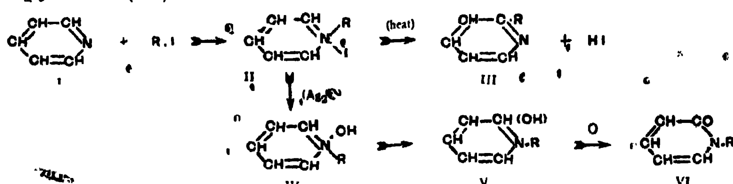


Pyridine itself is a colourless liquid, quite soluble in water, with a peculiar pungent odour somewhat reminiscent of ammonia. Its general properties may be taken as typical of those of its homologues. It is a strong base, and forms well-defined salts, many of which are, however, deliquescent. Its *platinichloride*, *aurichloride*, or *mercurichloride* are characteristic insoluble compounds. Two of the reactions of pyridine serve as reminders of the presence in its molecule of a tertiary nitrogen atom: it readily combines with α-halogen aliphatic acids, producing *pyridine-betaines*,

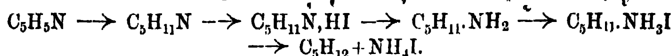


and, similarly, it forms quaternary halides with alkyl halides. The resulting *pyridinium halides* (II) show a tendency intramolecularly to rearrange themselves. Thus, when strongly heated, halogen acid is eliminated, and *alkyl pyridines* (III) are produced (usually substituted in the α-position), and when treated with silver oxide, *pyridinium hydroxides* (IV) are formed, and these substances tend to change rapidly into α-hydroxy-*N*-

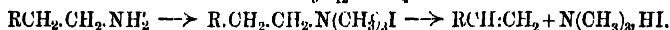
alkyl-dihydropyridines (V), which readily oxidize to *N-alkyl-α-pyridones* (VI):



Pyridine is much more readily reducible than benzene, and passes into piperidine when boiled with sodium and amyl alcohol. When it (or its homologues) is heated with hydriodic acid, aliphatic hydrocarbons and ammonia are produced. This reaction is readily understood when the similar decomposition of amines by "exhaustive methylation" is recollected:



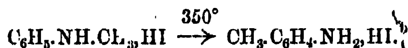
$C_5H_5N \longrightarrow C_5H_{11}N \longrightarrow C_5H_{11}N,HI \longrightarrow C_5H_{11}.NH_2 \longrightarrow C_5H_{11}.NH_3I \longrightarrow C_5H_{12} + NH_4I.$



$RCH_2.CH_2.NH_2 \longrightarrow R.CH_2.CH_2.N(CH_3)_3I \longrightarrow RCH{:}CH_2 + N(CH_3)_3,HI.$

It differs also from benzene in its susceptibility to substituting agents, for whilst the latter compounds can be readily halogenated, sulphonated, or nitrated, pyridine and its homologues cannot, except under certain special conditions regarding the nature and position of substituents (of a salt-forming nature), which must be previously present in the molecule. Halogen-substituted pyridines are, in fact, only obtainable by special syntheses (compare method (*c*) above), or from phosphorus halides and the pyridones.

On the other hand, a general similarity exists in many cases between the benzene and pyridine series; thus alkyl benzenes and alkyl pyridines are oxidized equally readily to carboxylic acids of their respective series, whilst amino-pyridines may be diazotized, etc., in the usual manner. The migration of alkyl groups from a pyridinium halide, forming alkyl pyridines, is also paralleled in the aromatic series, since substances of the type of methylaniline are transformed on heating with acid to a high temperature into homologues of aniline:



$$C_6H_5.NH.CH_3,HI \xrightarrow{350^\circ} CH_3.C_6H_4.NH_2,HI.$$

The more important bases are enumerated in the following table:

Pyridine, . . .	C_5H_5N		B.p. 117°.
Methylpyridines, . .	$C_5H_4(CH_3)N$	α-Picoline.	B.p. 130°. Oxidized by $KMnO_4$ to *picolinic acid.*
	,,	β-Picoline.	B.p. 1[illegible]3°. Occurs in distillate from cinchonine, strychnine, etc., when heated with lime. Oxidized to *nicotinic acid.*
	,,	γ-Picoline.	B.p. 144°. Oxidized to *isonicotinic acid.*
Dimethyl Pyridines,	$C_5H_3(CH_3)_2N$	Lutidines.	The 5 possible isomers are known.
Trimethyl Pyridines,	$C_5H_2(CH_3)_3N$	Collidines.	Some occur in decomposition products of alkaloids; others obtained synthetically.
Ethyl Pyridines, .	$C_5H_4(C_2H_5)N$	α and γ.	By heating pyridinium ethiodide.
	,,	β	From brucine, on boiling with potash.
Propyl Pyridines, .	$C_5H_4(C_3H_7)N$	α-*n*-Propyl.	*Conyrine*, from coniine and zinc dust.
	,,	α-*iso*-Propyl.	Synthetically from pyridinium isopropiodide.
Allyl Pyridines, .	$C_5H_4(C_3H_5)N$	α-Allyl.	By heating α-picoline and paraldehyde.

A few words must be given to the important *oxypyridines* (*pyridones*) and *pyridinecarboxylic acids.*

The *oxypyridines* are amphoteric compounds, possessing both basic nitrogen and acidic (phenolic) hydroxyl groups.

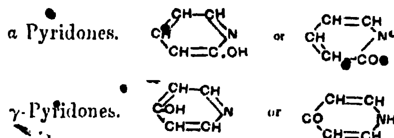
They are obtained by three general methods:

(*a*) The interaction of ammonia with α- or γ-pyrones.

(*b*) By heating oxypyridine carboxylic acids (from ammonia and pyrone carboxylic acids or their aliphatic generators).

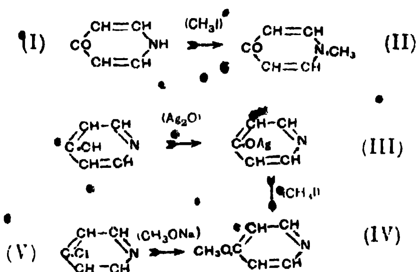
(*c*) By fusion of pyridine sulphonic acids with potash.

As already indicated, the pyridones may be considered according to either of two formulæ:



Their reactions point to the fact that these substances behave sometimes as oxypyridines and sometimes as pyridones; in other words, they are tautomeric. In the free state they behave more as oxypyridines than as lactams (pyridones), giving, for example, characteristic colours to ferric chloride solution. The nature of the tautomerism will be gathered from the following reactions of *γ-pyridone* (I):—

When this is heated with methyl iodide, *N-methyl-γ-pyridone* (II) is formed; but if the phenolic silver salt (III) is first prepared and then allowed to react with methyl iodide, there results *γ-methoxypyridine* (IV), identical with the substance obtained by heating *γ-chloropyridine* (V) with sodium methylate.



The chief oxypyridines are:

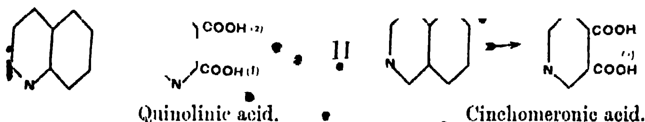
1-Oxypyridine.	α-Pyridone.	$C_5H_4(OH)N$.	M.p. 106°. From α-pyrone (coumalin) and ammonia.
2-Oxypyridine.	β-Pyridone.	,,	M.p. 124°. From pyridine β-sulphonic acid and fused potash.

3-Oxypyridine.	γ-Pyridone.	$C_5H_4(OH)N$	M.p. 148°. From γ-pyrone and ammonia.
2.4-Dimethyl-3-oxypyridone.	γ-Lutidone.	$C_5H_2(CH_3)_2(OH)N$.	M.p. 225°. From dehydracetic acid and ammonia
1.5-Dioxypyridine.	Glutaconimide.	$C_5H_3(OH)_2N$.	Of theoretical interest (compare p. 100).
1.3.5-Trioxypyridine.	Triketopiperidine.	$C_5H_2(OH)_3N$.	Analogue of phloroglucinol.

The great importance of the pyridine carboxylic acids lies in the fact that they are the most readily obtained derivatives from many complicated products of pyridine (such as the alkaloids), and hence are useful for the determination of the position of substituents.

The orientation of the three monocarboxylic acids of pyridine —*picolinic, nicotinic,* and *isonicotinic acids*—is therefore of fundamental importance, and is thus derived:

Quinoline (I) and isoquinoline (II) each yield *pyridine dicarboxylic acids* upon oxidation:



Quinolinic acid. Cinchomeronic acid.

These must therefore respectively be the 1.2- and 2.3-*dicarboxylic acids of pyridine*, and, when heated, they both lose carbon dioxide and form *mono*carboxylic acids.

Cinchomeronic acid (from isoquinoline) gives a mixture of nicotinic and isonicotinic acids, so that these two are either the β- or γ- acids respectively. Quinolinic acid, however, gives only one acid, nicotinic; and as this is also one of the products from cinchomeronic acid, it necessarily follows that *nicotinic acid* is the 2- or β-pyridine carboxylic acid. Hence *isonicotinic acid* is 3- or γ-pyridine carboxylic acid, and the remaining isomer, *picolinic acid*, must be the 1- or α-acid.

In addition to serving in general for the determination of substituent positions in complex pyridine derivatives, these acids were also employed originally to determine the configuration of the simple substitution products; thus the orientation of the picolines or methylpyridines was established by the fact that they can be oxidized to the corresponding pyridine carboxylic acids.

The *di-* and *tri-carboxylic acids* of pyridine have been orientated upon somewhat similar lines, but it is not necessary to consider these in detail.

These carboxylic acids are obtained, then, by the following general reactions :

(a) Oxidation of alkylpyridines.
(b) ,, ,, alkaloids such as quinine, cinchonine, brucine, strychnine, etc.
(c) (*Monocarboxylic* acids.) By heating the polycarboxylic acids.

They are crystalline, amphoteric compounds of fairly high melting-point, and, except for their feebly basic as well as acidic nature, resemble the benzene carboxylic acids very closely. A characteristic test for all α-carboxylic acids of pyridine is the reddish-yellow colour with ferrous sulphate.

The following table gives the more important pyridinic acids :

Monocarboxylic.	α- or 1-	Picolinic acid.	M.p. 135-136°.
	β- or 2-	Nicotinic acid.	M.p. 228-229°. From oxidation of *nicotine*; its methyl betaine is *trigonelline* (p. 40).
	γ- or 3-	Isonicotinic acid.	M.p. 304°. From cinchomeronic acid.
Dicarboxylic.	1.2-	Quinolinic acid.	M.p. 190°. From oxidation of quinoline.
	2.3-	Cinchomeronic acid.	M.p. 266°. From oxidation of cinchonine or isoquinoline.
	1.3-	Lutidinic acid.	M.p. 235°.
	1.5-	Dipicolinic acid.	M.p. 225°.
	2.4-	Dinicotinic acid.	M.p. 314°. From oxidation of corresponding lutidines.

Polycarboxylic.	1.2.3-	Carbocinchomeronic acid.	M.p. 250°. From oxidation of quinine or cinchonine.
	1.3.4-	Berberonic acid.	M.p. 235°. From oxidation of berberine.
	1.2.3.5-	(A tetracarboxylic acid.)	M.p. 227°.
	1.2.3.4.5-	(A pentacarboxylic acid.)	M.p. 220°.
Oxycarboxylic.	1-Oxy-4-	Oxynicotinic acid.	From ammonia and coumalic acid.
	3-Oxy-1-	Oxypicolinic acid.	From ammonia and comanic acid.
	3-Oxy-1.5-	Chelidamic acid.	From ammonia and chelidonic acid.

III. QUINOLINE AND ITS DERIVATIVES

We have already seen that there are two series of benzopyridines which correspond to naphthalene just as pyridine does to benzene, namely, one in which the α-, and the other in which the β-, methine group of the naphthalene nucleus is replaced by nitrogen; these series are respectively called *quinoline* (I) and *isoquinoline* (II).



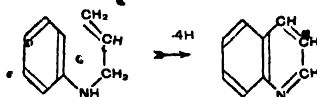


Both are found in the same circumstances as the simple pyridine bases, in bone-oil, coal-tar, and as decomposition products from various alkaloids, as will be shown in the next chapter. We shall confine ourselves for the moment to the *quinolines*, or *α-benzopyridines*, returning to the discussion of the remaining class a little later.

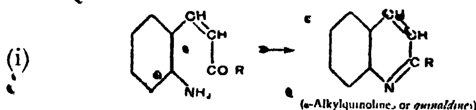
The constitution assigned to quinoline and its derivatives, already discussed on p. 101, rests mainly upon the variety of synthetic evidence which has gradually been collected.

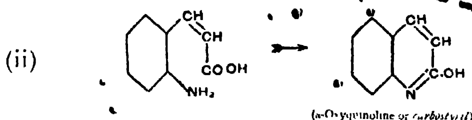
Some typical quinoline syntheses are as follows:—

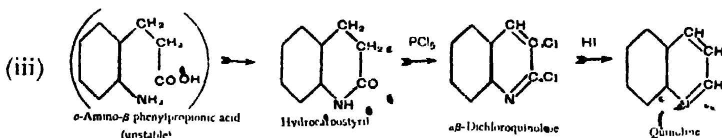
(*a*) By passing the vapours of allyl aniline over heated lead oxide:



(*b*) From *o*-aminocinnamic aldehyde (or ketones) by dehydration:

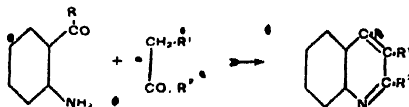
(i) 

(ii) 

(iii) 

Baeyer used the last reaction as proof of the structure of the quinoline ring-system.

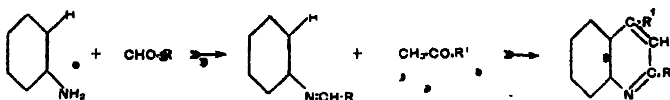
(*c*) From *o*-aminobenzaldehyde or *o*-aminobenzoketones by condensation with ketones, ketonic esters, or other compounds containing the $-CH_2.CO-$ group:



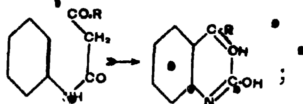
Thus acetone and *o*-aminobenzaldehyde give α-methylquinoline, *o*-aminoacetophenone and acetoacetic ester give a dimethylquinoline carboxylic ester, anthranilic acid and acetaldehyde yield γ-oxyquinoline, etc., etc.

(*d*) From aniline and its homologues by several means:

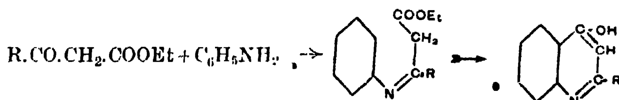
(i) Condensation with aldehydes and ketones in presence of mineral acid, oxidation taking place at the same time (Döbner-Miller):



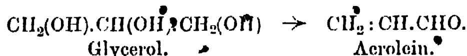
(ii) Condensation with β-ketonic esters; this is possible in two ways: An anilide may be formed by heating the ester with aniline, the condensation to an oxyquinoline being then effected with strong sulphuric acid (Knorr):



or, by allowing the first condensation to take place in the cold, the carbonyl group of the ester will be attacked in preference to the carbethoxyl; the action of heat on the unsaturated anilide derivative thus produced leads to the formation of oxyquinolines isomeric with those produced by Knorr's method:

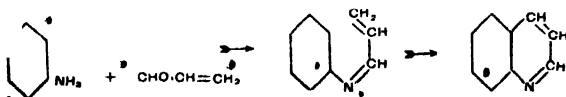


(iii) Condensation with glycerol in warm sulphuric acid solution in presence of a weak oxidizing agent, usually nitrobenzene (Skraup); this is probably the most widely applied quinoline synthesis, its mechanism being as indicated below:



$$CH_2(OH).CH(OH).CH_2(OH) \rightarrow CH_2:CH.CHO.$$

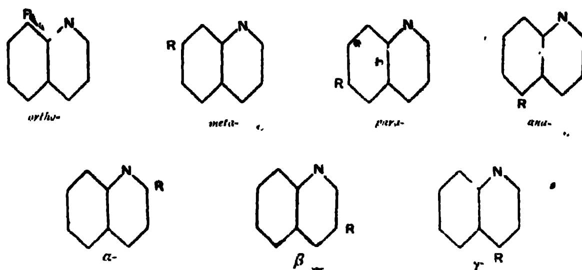
Glycerol. Acrolein.



(*e*) Just as pyrrol may be converted to pyridine, so indols are ultimately transformed to quinolines by the exhaustive action of alkyl iodides.

The main characteristics of the quinoline bases are the same as those of the pyridine series; they are, however, somewhat less

basic as a rule, and also less soluble in water. They yield betaines with halo-fatty acids, and iodalkylates with alkyl iodides. With respect to substitution, they combine the characteristics of both benzene and pyridine; thus the benzenoid part of the quinoline nucleus is as readily substituted by various groups as is benzene itself, whilst the nitrogenous ring is much less readily attacked. The various position isomerides are designated as follows:—



The α-, β-, or γ-haloquinolines are best prepared from the oxy-derivatives by the action of phosphorus halides. It is noteworthy that the substituents in α- or γ- substituted quinolines are abnormally reactive. For example, *quinaldine* or α-methylquinoline condenses like a ketone with aldehydes or ketones in presence of alcoholic alkalies:



$$(C_9H_6N).CH_3 + R.CHO \rightarrow (C_9H_6N).CH{:}CH.R.$$

Similarly, aniline and α- or γ-chloroquinoline react with elimination of hydrogen chloride:



$$(C_9H_6N).Cl + C_6H_5.NH_2 \rightarrow (C_9H_6N).NH.C_6H_5.$$

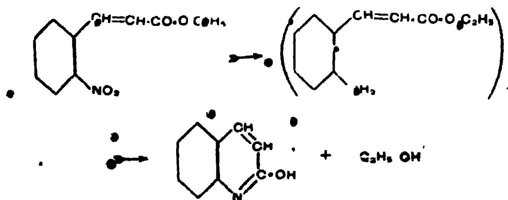
The following are the most interesting quinoline compounds:—

			Synthesized from
Quinoline	C_9H_7N	B.p. 239°. Methiodide, m.p. 72°. Dichromate, m.p. 165°	Aniline

			Synthesized from
α-Methylquinoline	$C_9H_6N(CH_3)$	*Quinaldine*, b.p. 247°	Aniline and paraldehyde.
γ- ,,	$C_9H_6N(CH_3)$	*Lepidine*, b.p. 257°	—
α-Phenylquinoline	$C_9H_6N(C_6H_5)$	M.p. 84°	Aniline and cinnamaldehyde.
α-Oxyquinoline	$C_9H_6N(OH)$	*Carbostyril*, m.p. 199°	See below.
γ- ,,	,,	*Kynurin*, m.p. 201°	—
o-, m-, and p- Oxyquinoline	,,	—	o-, m-, and p- aminophenols.
α-Chloroquinoline	$C_9H_6N(Cl)$	M.p. 38°, b.p. 267°	Carbostyril and PCl_5.
β- ,,	,,	B.p. 255°	Quinoline and SCl_2.
γ- ,,	,,	M.p. 34°	γ-Oxyquinoline.
α-Aminoquinoline	$C_9H_6N(NH_2)$	M.p. 114°	α-Chloroquinoline.
α-Quinoline carboxylic acid	$C_9H_6N(COOH)$	*Quinaldic acid*, m.p. 156°	Quinaldine by oxidation.
γ- ,, ,,	,,	*Cinchoninic acid*, m.p. 254°. From cinchonine by oxidation with potassium permanganate	Lepidine by oxidation.
o-, m-, and p- carboxylic acid	—	—	o-, m-, and p-aminobenzoic acids.
α,β Quinoline dicarboxylic acid	$C_9H_5N(COOH)_2$	*Acridinic acid*, m.p. 130°. From acridine and $KMnO_4$	—

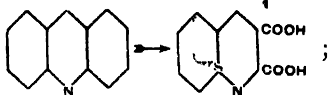
One or two of these compounds merit a little further attention.

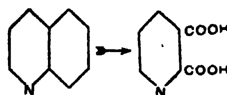
α-Oxyquinoline, carbostyril, in addition to being obtained from α-chloroquinoline on boiling with water, may be directly synthesized by the reduction of o-nitrocinnamic ethyl ester, since it is the *lactam* (p. 29) of o-aminocinnamic acid:



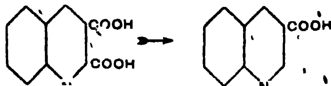
Like the pyridones, the α- and γ-oxyquinolines yield both *O-alkyl ethers* (from the silver salts and alkyl iodides, and from α- or γ-chloroquinolines and sodium alkylates) and *N-alkyl ethers* (from the action of alkyl iodide in presence of aqueous alkali).

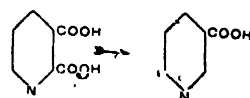
The production of *acridinic acid* from acridine is similar to that of *quinolinic acid* from quinoline:



;


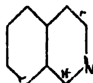
and, just as the latter acid on heating loses carbon dioxide and forms *nicotinic acid*, so acridinic acid forms β-quinoline carboxylic acid when heated to its point of fusion:





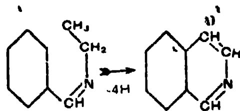
IV. Isoquinoline and its Derivatives

The structure assigned to isoquinoline,

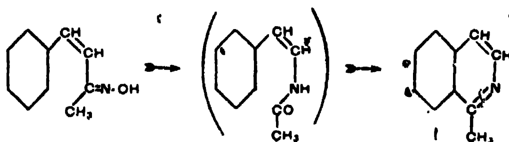


is confirmed by the following syntheses:—

(*a*) Of *isoquinoline* on passing benzylidene-ethylamine through red-hot tubes:—

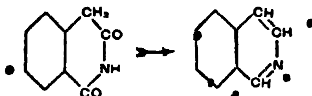


(*b*) Of *methyl isoquinoline* from benzylideneacetoxime upon heating with phosphoric anhydride (by means of the Beckmann rearrangement):

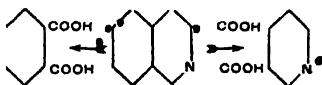


(c) Of *isoquinoline* from β-naphthoquinone.

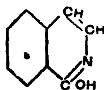
(d) Of *isoquinoline* by distilling homophthalimide and zinc dust :—



The correctness of this view is further borne out by the oxidizing action of potassium permanganate upon isoquinoline, when both *phthalic* and *cinchomeronic* acids are formed.



Chemically speaking, isoquinoline (m.p. 23°, and b.p. 240°) is exactly similar in behaviour to quinoline itself. It forms analogous derivatives (betaines, alkiodides, etc.), and its substitution products are produced by the same methods, and react in precisely the same manner as the corresponding quinoline compounds. For example, *isocarbostyril*,



yields *N-alkyl ethers* with alkyliodides and alkalies, or *O-alkyl ethers*, with alkyl iodides and its silver salt, thus exhibiting the usual tautomerism.

The following are the chief derivatives :—

a Methylisoquinoline, $C_9H_6N(CH_3)$. See synthesis above.

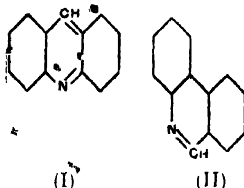
aβ-Dichloroisoquinoline, $C_9H_5NCl_2$. From homophthalimide and phosphorus chloride.

a-Oxyisoquinoline, $C_9H_6N(OH)$. See above.

V. Acridine and other Complex Benzopyridine Compounds

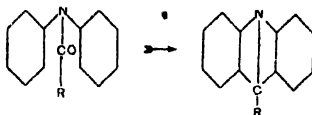
Many ring systems can be built up from annealed benzene, quinoline, and isoquinoline nuclei, and quite a number have been

met with, either as coal-tar products or by synthetic processes. Only two, however, are of especial importance, namely, *acridine* (I) and *phenanthridine* (II).

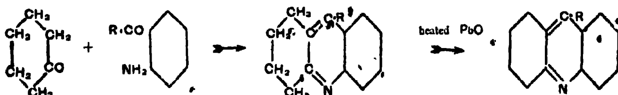


Acridine may be regarded either as a symmetrical benzoquinoline, or as bearing to anthracene the same relation that pyridine does to benzene. The following syntheses are typical of those used in the preparation of acridine derivatives :—

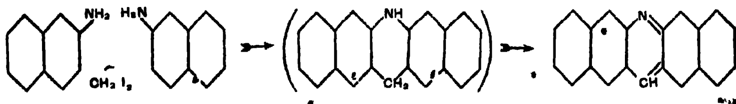
(*a*) Condensation of *N* acyldiphenylamines by heating with zinc chloride :



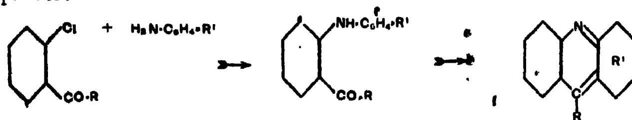
(*b*) Condensation of cyclohexanones with *o*-aminoaryl ketones :



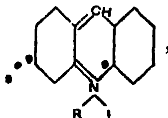
(*c*) Condensation of methylene halides with aromatic aminocompounds :



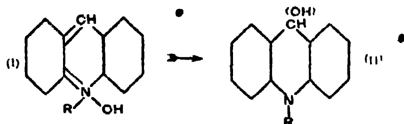
(*d*) Condensation of anilines with *o*-chloroarylketones by means of copper powder :



Acridine is less basic than quinoline or pyridine, and in physical contrast to these is a solid, of fairly high melting-point, with exceedingly irritating action on the skin and eyes. Solutions of its salts are fluorescent (bluish-green). It is oxidized by permanganate to acridinic acid (quinoline $\alpha\beta$-dicarboxylic acid) and $\alpha\beta\alpha^1\beta^1$-pyridinetetracarboxylic acid. It forms *alkyliodides* of the formula

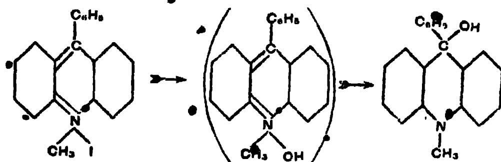


and these, by treatment with silver oxide, furnish unstable *ammonium bases* (I), which spontaneously rearrange themselves to ψ-*bases* of the structure II below.



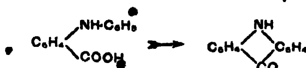
In presence of strong mineral acids, the ψ-bases are transformed into salts of the ammonium (or *acridinium*) type.

Hantzsch studied these phenomena quantitatively by means of electrical conductivity measurements based upon *ms*-phenyl acridine methiodide:—

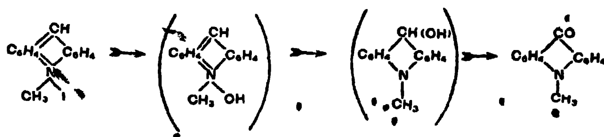


The *ms-oxyacridines* or *acridones* are somewhat similar in their tautomeric behaviour to carbostyril and the pyridones, but are more definitely ketonic in their general behaviour. The simplest member, *acridone*, may be produced:

(*a*) From phenylanthranilic acid and sulphuric acid:



(*b*) As the *N-methyl* derivative, from methyl acridinium iodide in presence of silver oxide and a mild oxidizing agent:



It is a very stable substance, melting at 354°, and yields *ms*-chloroacridine, $C_6H_4 <\!\!\frac{CCl}{N}\!\!> C_6H_4$, by the action of phosphorus trichloride, whilst acridine is formed when it is distilled with zinc dust.

The chief acridine compounds are:

Acridine.	$C_{13}H_9N$.	M.p. 110°.	
ms-Methylacridine.	$C_{14}H_{11}N$.	M.p. 114°.	From acetyldiphenyl amine.
2.7-Dimethylacridine.	$C_{15}H_{13}N$.	M.p. 171°.	From *p*-toluidine and methylene iodide.
ms-Phenylacridine.	$C_{19}H_{13}N$.	M.p. 181°.	From benzoyldiphenyl amine.
Acridone.	$C_{13}H_9ON$.	M.p. 354°.	
N-Methylacridone.	$C_{14}H_{11}ON$.	M.p. 203°.	
Quinacridine.	$C_6H_4 <\!\!\frac{CH}{N}\!\!> C_6H_2 <\!\!\frac{N}{CH}\!\!> C_6H_4$	M.p. 218°.	From phloroglucinol and anthranilic acid with zinc dust.

The isomeride of acridine, *phenanthridine*, may be regarded either as an unsymmetrical benzo-quinoline or as a benzo-isoquinoline, and as being related to phenanthrene in the same way that acridine is to anthracene.

It may be synthesized:

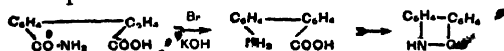
(*a*) By passing benzalaniline through red-hot tubes:



(*b*) By heating acyl-*o*-aminodiphenyls:

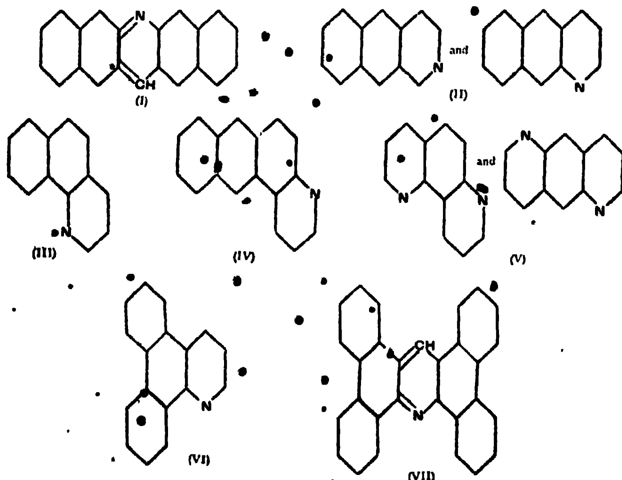


Phenanthridone, $\begin{array}{c}C_6H_4—C_6H_4\\ |\quad\quad | \\ NH—CO\end{array}$, resembles acridone closely, and is produced by mild oxidation of phenanthridine (into which it repasses on distillation with zinc dust) and by synthesis from the monamide of diphenic acid:



By means of Skraup's reaction or the methylene iodide synthesis, a number of more complex acridine-like compounds have been obtained, of which the following are the chief types :—

I.	*Naphthacridines.*	From naphthylamines and methylene iodide.
II.	*Anthrapyridines.*	From *N*-benzoylpyridine acids.
III.	*Naphthoquinolines.*	From naphthylamines by Skraup's reaction.
IV.	*Anthraquinolines.*	From aminoanthracenes by Skraup's reaction.
V.	*Phenanthrolines.*	From *m*- and *p*- phenylenediamines by Skraup's reaction.
VI.	*Phenanthraquinolines.*	From aminophenanthrenes by Skraup's reaction.
VII.	*Phenanthracridines.*	From aminophenanthrenes and methylene iodide.



VI. Quinoline and Acridine Dyes

Certain derivatives of the ring systems discussed in the three preceding sections have found application as dyes, although at the present day the cost of their production inhibits their extended use. The following are the most notable :—

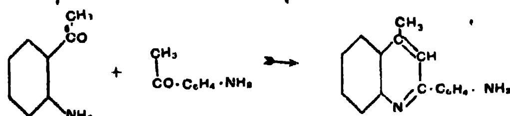
A. From quinoline :

(*a*) *Quinoline yellow*, formed by fusing quinaldine with phthalic anhydride, and sulphonated before use as a dye.



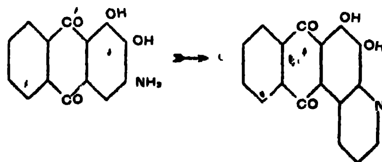
(*b*) *Quinoline red*, formed in a similar manner to malachite green by fusing quinaldine and *iso*quinoline with zinc chloride.

(*c*) *Flavaniline*, a bright yellow dye, from the zinc chloride condensation of a mixture of *o*- and *p*- aminoacetophenones,



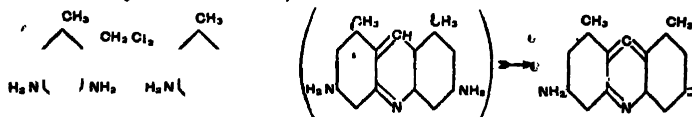
(*d*) *Alizarin blue*, *alizarin green*, *alizarin indigo*, etc., etc.

Different sulphonic acids and polyoxyderivatives of the substance produced from aminoalizarin by the Skraup synthesis ; these dyes are easily reduced to leuco-compounds, which readily re-oxidize in the air :—

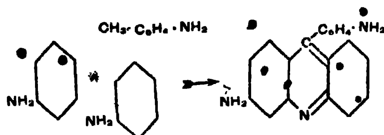


B. From acridine :—

(*a*) *Acridine yellow*, produced by condensation of methylene dichloride with *m*-toluylenediamine :

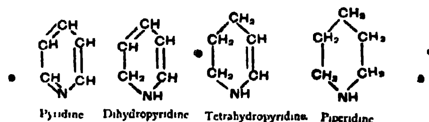


(*b*) *Chrysaniline*, a fine yellow dye, occurs in commerce as phosphine, and is a bye-product in the manufacture of pararosaniline. It is chiefly used in polishes, and is probably formed as follows:—

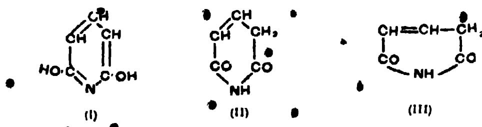


VII. Piperidine, Tetrahydroquinoline, and Dihydroacridine

Pyridine is very similar to pyrrol in its behaviour towards alkaline reducing agents; obviously it can be reduced in three stages, and derivatives of each of these are known:



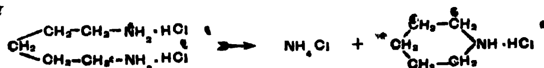
As may frequently be noticed in similar series of compounds, it is only the extreme members which are stable and well defined. The dihydropyridines reoxidize exceedingly readily to pyridines, although the tetrahydro-compounds are more stable. The only important derivatives of the latter class, however, are the *keto-tetrahydropyridines*; these are, as a matter of fact, identical with the dioxypyridines if the latter exist in the ketonic form. Thus aa^1-dioxypyridine (I), 1.5-diketotetrahydropyridine (II), and the imide of glutaconic acid (III) are different names for the same substance:



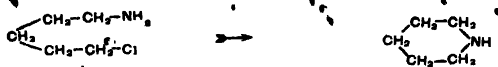
The ultimate reduction product, *piperidine*, is very important. It occurs in nature combined with piperic acid, as *piperine* (in

pepper), and has been prepared synthetically by the following methods :—

(*a*) Distillation of pentamethylene diamine hydrochloride :



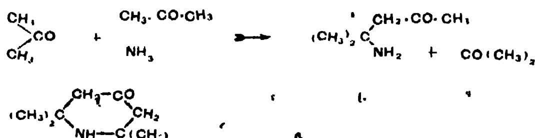
(*b*) The action of hot dilute caustic potash on ε-chloroamylamine :



Piperidine is a strongly basic liquid, readily soluble in water, b.p. 105°. It reacts as a typical secondary aliphatic amine, yielding *N*-alkyl and *N*-acyl derivatives in the usual way. It is strange to find, however, that not only alkyl iodides, but also aryl halides react with piperidine (forming *N*-arylpiperidines).

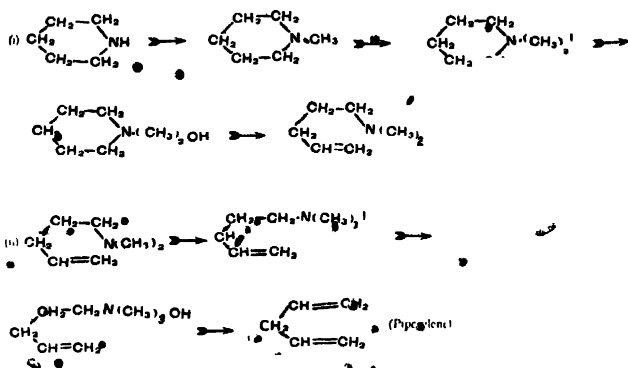
This abnormal behaviour ceases, however, as soon as substituents are introduced into the piperidine ring. Whilst *N*-substituted piperidines are thus obtained by methods characteristic for compounds containing the group $-CH_2-NH-CH_2-$, the *C*-substituted derivatives (alkyl-, oxy-, carboxy-, etc., etc.) are best prepared by the reduction of the corresponding pyridine compounds by sodium and amyl alcohol.

The production of a ketopiperidine compound by the condensation of acetone with ammonia is noteworthy :



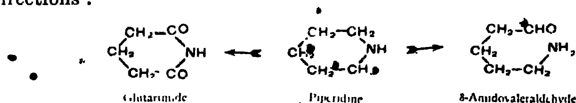
Remembering that piperidine is converted on the one hand to pyridine by mild oxidation, it is instructive to observe that on the other it may be broken down into various aliphatic open-chain compounds as follows :—

(*a*) By exhaustive methylation, in the customary manner, and according to the following scheme :—

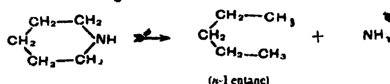


It will be recollected that pyrrolidine suffers a similar change; whilst by interrupting the reaction at the end of stage (i), and allowing the unsaturated ammonium base to interact with hydrogen chloride, a condensation to a *methyl-pyrrolidine* takes place.

(*b*) By oxidation with hydrogen dioxide; this reaction takes place in two directions :

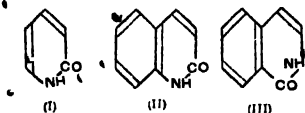


(*c*) By reduction with hydriodic acid in sealed tubes :



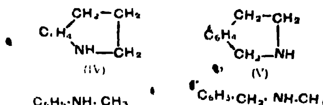
The reduction products of quinoline and of isoquinoline may be profitably discussed together. Similarly to the corresponding pyridine derivatives, the *dihydro-quinolines* and *-isoquinolines* are very unstable bodies, readily reverting to the aromatic state; but it must be remembered that just as the mono-oxypyridines frequently behave as ketodihydropyridines (I), so, for example,

carbostyril and isocarbostyril may often be regarded respectively as ketodihydroquinoline (II) and ketodihydroisoquinoline (III).



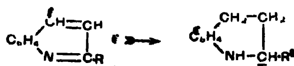
When either quinoline or isoquinoline is heated with sodium and amyl alcohol, four atoms of hydrogen are absorbed, and the pyridine nucleus is fully hydrogenized, but the benzenoid residue remains unattacked.

The resulting bases, *tetrahydroquinoline* (IV) and *tetrahydroisoquinoline* (V), are strongly basic liquids with penetrating smells. They are both secondary amines, and furnish *N*-nitroso-, *N*-benzoyl-, and *N*-alkyl-derivatives in the manner characteristic of such substances. A glance at their respective formulæ shows, however, that, whilst tetrahydroquinoline corresponds, for example, in some degree to methylaniline, tetrahydroisoquinoline is more like methylbenzylamine :–



and this anticipation proves correct, for tetrahydroisoquinoline, like the benzylamines, is an exceedingly strong base forming a stable carbonate, whilst tetrahydroquinoline, although markedly basic, partakes more of the nature of ethylaniline in its chemical behaviour.

Most of the important quinoline bases and their substituted derivatives have been reduced to the corresponding tetrahydro-compounds, and in some of these, naturally, an asymmetric carbon atom results by this process :

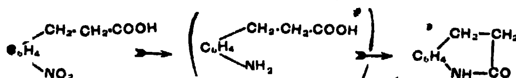


In a few cases (notably *tetrahydroquinaldine*, $C_9H_{10}N.CH_3$) the racemic compounds obtained on reduction have been resolved into their *d*- and *l*- con-

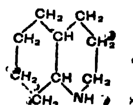
stituents by fractional crystallization of their salts with an optically active acid (tartaric or β-bromocamphorsulphonic).

N-methyltetrahydroquinoline finds application as a febrifuge under the name of *kairoline.*

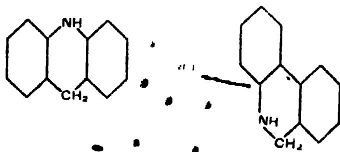
It may be recollected, finally, that the *lactams* of *o*-amino-β-phenylpropionic acids are ketotetrahydroquinolines (or dihydrocarbostyrils).



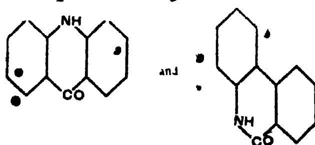
It appears possible, by careful application of strong reducing agents such as phosphorus and hydriodic acid, to obtain hydroquinolines hydrogenized in both ring-systems, the final product being *deca-hydroquinoline*,



The reduction of acridine and phenanthridine (either by sodium and alcohol, or by tin and hydrochloric acid) only leads to the production of *dihydro*-compounds, hydrogen being added to the – N – CH – system :—



These substances are colourless, non-basic, non-fluorescent bodies, which re-oxidize, in presence of atmospheric oxygen, to the respective aromatic compounds; they also reduce ammoniacal silver solution, forming the same products. As usual it is possible to regard the *ms*-oxyderivatives of the aromatic compounds (acridones and phenanthridones) as keto-derivatives of the dihydro-reduction products:



VIII. Some Simple Naturally-Occurring Derivatives of Pyridine

The intimate relation of pyridine, quinoline, and isoquinoline to the important complicated nitrogen bases occurring in many plants, and classified as the "alkaloids," has already been emphasized. The complex nature and molecular magnitude of most alkaloids makes it necessary to devote a separate chapter to the special methods in use for the elucidation of their structure; there are, however, a few alkaloids which are relatively simple in constitution and very closely allied to pyridine or its reduction product, piperidine. In order, therefore, to preserve the sequence followed in other chapters of the part of this book dealing with heterocyclic compounds, we will describe the most interesting of these simpler alkaloids by way of concluding this section. Some of them, indeed, have already been mentioned with the betaines (chap. iii., p. 40); these include *arecoline*, *arecaidine*, *trigonelline*, and *apophyllenic acid*. Three others are of especial interest, namely, *piperine*, *conine*, and *nicotine*.

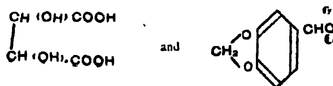
Piperine, $C_{17}H_{19}O_3N$, is a white solid occurring (about 7-9 per cent.) in pepper. It barely shows basic properties, but is decomposed by hot alcoholic alkali into the salt of *piperic acid*, $C_{12}H_{10}O_4$, and the strong base *piperidine* (p. 122). Cold alkali does not decompose it, however, and it therefore appears to be, not the piperidine salt, but the *piperidide*, of *piperic acid*. The analytical and synthetic evidence of the structure of the acidic and basic parts of the compound confirm this view and demonstrate the ultimate structure of the compound.

A. (*a*) We have seen that piperine may be decomposed into equimolecular proportions of piperidine and piperic acid.

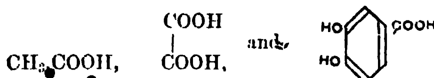
(*b*) The analytical proof of the structure of *piperidine* is given on p. 123.

(*c*) *Piperic acid* absorbs four atomic proportions of bromine, and therefore may be supposed to contain two ethenoid bonds $-CH=CH-$ and $-CH=CH-$.

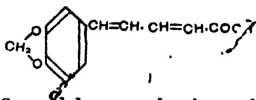
(*d*) The acid is oxidised by cold dilute permanganate to a mixture of racemic acid and piperonal:



(*c*) Fusion of the acid with potash yields a mixture of acetic, oxalic, and protocatechuic acids :



Bearing in mind the molecular formula, this leads to the following structure for *piperic acid* :—

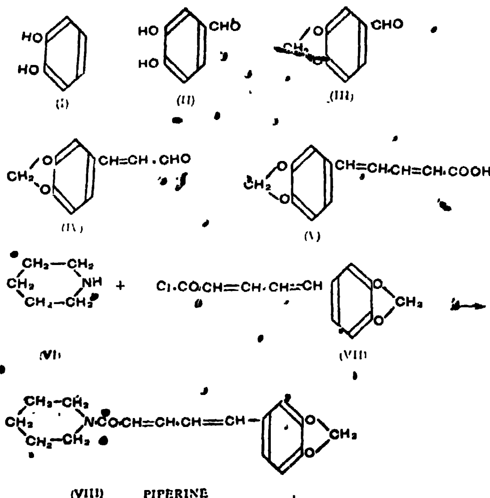


This has been confirmed by synthesis as follows :—

B. (*a*) *Pyrocatechol* (I) was converted to *protocatechuic aldehyde* (II) by heating with chloroform and caustic potash (Reimer's reaction) ; this was then treated with methylene iodide and silver oxide, producing the methylene ether of the aldehyde, *piperonal* (III). By condensation with acetaldehyde in presence of dilute alkali, this yielded *piperonylacrolein* (IV), which gave *piperic acid* (V) (by Perkin's reaction) on heating with sodium acetate and acetic anhydride.

(*b*) The synthesis of *piperidine* (VI) has been given on page 122.

(*c*) The *chloride* of *piperic acid* (VII), when heated with *piperidine*, gave *piperine*, identical with the natural alkaloid, which therefore possesses formula VIII.



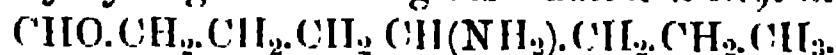
Coniine, $C_8H_{17}N$, is an optically active liquid, boiling at 167°, which occurs in hemlock, and imparts to that plant its characteristic heavy odour and poisonous, stupefying properties. The natural product is *dextrorotatory*, but Ladenburg synthesized both racemic, *lævo-* and *dextro-* forms in 1886 (the first complete laboratory synthesis of an alkaloid).

The probable composition of coniine is shown by the following typical decompositions:

(*a*) Reduction with phosphorus and hydriodic acid gives *normal octane*, C_8H_{18}, and ammonia.

(*b*) Distillation with zinc dust yields a *propyl pyridine* ("*a-conyrine*"), which reverts to coniine by alkaline reduction, but by further oxidation gives *picolinic acid* (p. 108). The propyl group is, therefore, in the α-position to the nitrogen atom, and, from reaction (*a*), is probably a normal propyl radicle, $CH_3.CH_2.CH_2-$. This view is confirmed by the synthetic production of α-propyl pyridine, identical with α-conyrine.

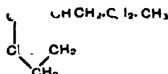
(*c*) Oxidation by hydrogen dioxide gives *δ-amido-n-octyl aldehyde*,



(*d*) "Exhaustive methylation" (compare pp. 53, 123) leads to the production of *conylene*, an unsaturated *n*-propylamylene of the structure



Coniine is accordingly most probably to be formulated as *d-α-n-propylpiperidine.*

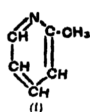


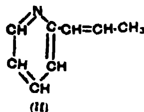
Ladenburg's synthesis confirms this view:

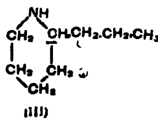
(*a*) We may presuppose the synthesis of *pyridine* from its elements by the intermediate stages of carbon disulphide, acetic acid, acetone, glycerol, trimethylene bromide and cyanide, pentamethylene diamine, and *piperidine*.

(*b*) By methylation and subsequently heating at 300°, pyridine yields α-methylpyridine (I) (α-picoline, p. 105), which, being an α-substituted alkylpyridine, condenses with acetaldehyde to α-propenylpyridine (II). This substance on reduction at a high temperature passes into *racemic coniine* (III).

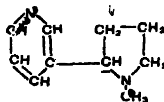
(*c*) By fractional crystallization of the *d*-tartrates of $(d+l)$-coniine, the optical antipodes may be separated.







Nicotine, $C_{10}H_{14}N_2$, is a liquid alkaloid, boiling at 247°, and *lævo*-rotatory, and occurs in tobacco-leaves to the extent of between one and eight per cent., the better tobaccos containing least nicotine. It is a ditertiary base, and is usually present in the tobacco-plant as malate or citrate. It is miscible in most proportions with water, possesses a pungent smell, and is very poisonous. Although discovered in 1828, its constitution was not cleared up till about 1891-1895, when Pinner showed it to be *a-β pyridyl-N-methylpyrrolidine*.



Confirmatory synthetic evidence for this formula was arrived at by Amé Pictet and his students in 1904, after ten years' preliminary work on the subject.

The following are the chief decomposition reactions of nicotine:

(*a*) It is a ditertiary base, and forms two isomeric non-identical *methiodides*.

(*b*) Distillation with zinc-dust gives both *pyrrol* and *pyridine*.

(*c*) Reduction by sodium and alcohol gives *hexahydronicotine*, $C_{10}H_{20}N_2$.

(*d*) Mild oxidation (silver oxide) produces a base *nicotyrine*, $C_{10}H_{10}N_2$.

(*e*) Stronger oxidation (nitric or chromic acids, or permanganate) gives only *nicotinic acid* (pyridine-β-carboxylic acid).

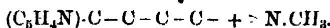
(*f*) Bromine water gives two *dibromo*-oxidation products, one of which, when hydrolysed by alkali, forms *methylamine* and *oxalic acid*, and the other by similar treatment is decomposed into *nicotinic acid*, *methylamine*, and *malonic acid*.

This evidence has been applied as follows:—

(i) Reactions (*b*) and (*e*) indicate the presence of a *pyridine ring system*.

(ii) Reaction (*e*) suggests that the remainder of the molecule is attached to the pyridine nucleus by means of an *alkyl* group in the β-position.

(iii) Reaction (*f*) shows that the non-pyridine nitrogen atom must b united to a *methyl* group, and that the substituent group in the pyridine nucleus must contain the skeletons -C - C- and -C – C-C-, so that we have:



$$(C_5H_4N)\text{-}C-C-C-C-+>N.CH_3.$$

(iv) Remembering that reaction (*b*) indicates the presence of a *pyrrol* system, we may combine these facts as in the above formula for nicotine, where it appears that the pyrrol residue is hydrogenized, a fact which explains the production of basic *nicotyrine* by mild oxidation (*d*).

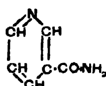
The synthesis of nicotine was accomplished by the following series of reactions :—

(*a*) The amide of nicotinic acid (I) was converted to *β-amino-pyridine* (II) by Hofmann's reaction.

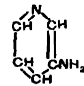
(*b*) The latter compound was distilled with mucic acid, leading (as on p. 42) to the formation of *N-β-pyridylpyrrol* (III) ; on passing this through red-hot tubes it was rearranged (compare alkyl-pyrrolium halides, p. 53) to *α-β-pyridylpyrrol* (IV).

(*c*) This was treated with methyl iodide, when a compound identical with *nicotyrine methiodide* resulted, from which *nicotyrine* (V) was obtained by the action of potash, thus showing that substance to be *α-β-pyridyl-N-methylpyrrol* (V).

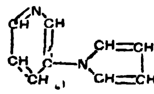
(*d*) The last step in the synthesis is the reduction of the pyrrol residue without simultaneous alteration of the pyridine part of the molecule. This is impossible by the usual method of heating with sodium in alcohol, since reduction takes place throughout, and *hexahydronicotine* is produced. If, however, nicotyrine is treated with iodine, a *monoiodonicotyrine* is formed, which is reducible by tin and hydrochloric acid to *dihydronicotyrine* (VI). The latter compound absorbs two atoms of bromine, and the resulting product is again reduced by tin and hydrochloric acid, when inactive *nicotine* (VII) is formed. Pictet, having pursued the synthesis thus far, completed it by desolving the inactive base into its *d*- and *l*- forms by means of the *d*-tartaric acid salt.



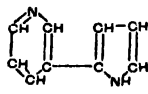
(I)



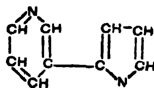
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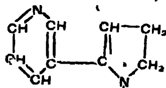
(III)



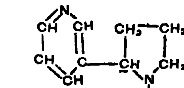
(IV)



(V)



(VI)



(VII) NICOTINE

CHAPTER VIII

THE ALKALOIDS

I. General.

IT will be best, before describing the remaining classes of heterocyclic compounds, to deal at this point with the extensive group of naturally occurring derivatives of pyridine, quinoline, pyrrol, etc., which have come to be known as the "alkaloids" or plant bases.

These substances occur in various plants, and, as a rule, the same alkaloid is found to occur only in closely allied plants: thus nicotine is found only in *Nicotiana* species, piperine only in the seeds of different varieties of pepper, and so on. The physiological effect of different plants or plant-juices (for example, the poison in hemlock, the medicinal utility of cinchona bark, or the hypnotic influence of opium) has been known in some cases for hundreds of years, but the causes of these phenomena were not traced until towards the close of the eighteenth century, when Hoffmann stated that he had obtained crystals from cinchona bark. A few years later, about 1810, Sequin investigated a similar crystalline product from opium, and, apparently during the next decade or so, these discoveries received considerable attention, for within this period the following alkaloids were isolated in a more or less pure state:—

	Alkaloid.	*Source.*	*Isolated by*
1817.	Morphine.	Opium.	Seturner.
1818.	Strychnine.	Nux vomica.	Pelletier and Caventou.
1819.	Brucine.	,,	,, ,, ,,
1819.	Piperine.	Pepper.	Oersted.
1820.	Quinine.	Cinchona bark.	Pelletier and Caventou.
1821.	Cinchonine.	,,	,, ,, ,,
1827.	Coniine.	Hemlock.	Giesecke.
1828.	Nicotine.	Tobacco.	Posselt and Reiman.

The empirical formulæ of most of these compounds were worked out, mainly by Liebig and his students, between 1825 and 1850, together with some of their chief chemical decompositions. It was thus observed that many members of the group gave, by destructive distillation, *pyridine* or *quinoline*—bases which were receiving considerable attention at about this period (1850). Hence the alkaloids were defined as *complex naturally occurring pyridine bases.*

Later research showed that a number of other heterocyclic ring-systems entered into the composition of many alkaloids, and therefore this definition could not be maintained. At the present time, it is usual to refer *any cyclic nitrogenous compound found in nature* to the class of alkaloids, so that the term embraces not only the complicated pyridine, etc., bases, but also bases such as creatine (p. 193) or caffeine (p. 193), and other compounds, such as pilocarpine (p. 74) and uric acid (p. 196).

In this chapter, however, we shall confine our attention to the complex basic alkaloids derived from the heterocyclic systems already discussed, and leave substances of the type of creatine, caffeine, and uric acid to a succeeding chapter (X.).

Structural formulæ for the alkaloids now under consideration are of comparatively recent date; indeed, in a few cases these are still uncertain. The first to be definitely settled were two of the simplest, *piperine* and *coniine.* The structure of the latter was confirmed by a synthesis by Ladenburg in 1886, and this represents the first synthetical evidence on the subject.

Greater progress has been made since about 1895 with regard to the ultimate structure of alkaloids, both from the synthetical and analytical sides; and we may summarize the position at the present date (1911) as follows :—

Alkaloids completely synthesized: Piperine, coniine, nicotine, atropine, cocaine, meconine, narcotine, narceine, papaverine, and hydrastine.

Alkaloids whose structure is known with tolerable certainty: Berberine, quinine, cinchonine, cinchonidine, and conchinine.

Alkaloids of uncertain structure: Morphine, codeine, thebaine; strychnine, brucine, sparteine, aconitine.

It is obvious that these substances may be classified according

to the heterocyclic ring-systems from which they are ultimately derived; but inasmuch as a considerable number possess more than one type of ring-system in the molecule this method is of little use as a practical guide. We shall therefore discuss the few typical members which space permits according to the plant families to which each group (as indicated above) is peculiar, and for our purpose we may make a rough classification as follows:—

Plant Families.	*Alkaloids.*
Piper (Pepper).	Piperine ; } (see chapter VII, pp. 126-130).
Conium (Hemlock).	Coniine }
Nicotiana (Tobacco).	Nicotine }
Solanum (Nightshade).	Atropine, hyoscine (cocaine).
Papaver (Poppy).	Meconine ; narcotine, narceine, papaverine ; morphine, thebaine, codeine.
Berberis (Barberry).	Hydrastine, berberine.
Cinchona.	Quinine, cinchonine, cinchonidine, conchinine
Strychnos (Nux Vomica).	Strychnine, brucine.

We will next indicate the different ring-systems embodied in these alkaloids, and here we must distinguish between the presence of *isolated* ring-systems and those composed of fused or "*annealed*" nuclei (just as quinoline is made up of a benzene residue "annealed to" a pyridine group).

A. Isolated Ring-Systems

(*a*) *Pyridine.*	Piperine, coniine, nicotine.
(*b*) *Pyrrol.*	Nicotine.
(*c*) *Quinoline.*	Quinine, cinchonine.
(*d*) *Iso-Quinoline.*	Papaverine, narcotine, hydrastine.
(*e*) *Lactone.*	Pilocarpine.

B. Annealed Ring-Systems

(*a*) *Betaine.*	Trigonelline, arecoline, strychnine, brucine.
(*b*) *Pyridine.*	Trigonelline, arecoline, atropine, cocaine, quinine, cinchonine.
(*c*) *Pyrrol.*	Atropine, cocaine.
(*d*) *Quinoline.*	Strychnine, brucine.
(*e*) *Carbazole.*	Strychnine, brucine.
(*f*) *Phenanthrene.*	Morphine, thebaine, codeine.
(*g*) *Oxazine* (*para*-).	Morphine, thebaine, codeine.

In many cases the above heterocyclic nuclei are present in the reduced state; thus the *pyridine* group is represented as *piperidine* in piperine, coniïne, atropine, and quinine, and the *pyrrol* residue is similarly present in the form of a *pyrrolidine* ring in nicotine and atropine, whilst *isoquinoline* appears in narcotine as a substituted *tetrahydroisoquinoline.*

A few words must be added on the general physical and chemical characteristics of the alkaloids.

In the first place, it is generally believed that the alkaloids are formed in the plant tissues (usually in the *fruit* or *sap*) as by-products in the decomposition of still more complicated products of the organism, just as uric acid is secreted by carnivorous, and hippuric acid by herbivorous, mammalia.

It is also supposed that what we term alkaloids are really derivatives of slightly more simple compounds, the latter being the real by-products referred to in the last sentence. It is well known that, for example, benzaldehyde cyanhydrin (mandelonitrile) is not deposited as such in the almond, but reacts with glucose present in the juice to form a glucoside. In the same way a very few alkaloids are found in the form of glucosides, but the majority appear to have condensed with other constituents of the plant juice in either of the two following ways:—

(i) With an *organic acid* to produce an *ester*. (Atropine or piperine.)
(ii) With *formaldehyde* yielding a *methyl ether*. (Narcotine, quinine, brucine, cocaine, etc., etc.)

It is significant that the only alkyl ethers found in alkaloids are as a matter of fact *methyl* ethers; whilst progressive stages of methylation may often be noticed in alkaloids which occur together in one plant. A few examples are:—

Brucine (dimethoxy-strychnine).
Quinine (methoxy-cinchonine).
Codeine (methylmorphine, and thebaine (dimethylmorphine).

Turning to general physical properties, we find that, with the exception of a few high-boiling liquids (*coniine, nicotine, arecoline*), the alkaloids are colourless crystalline solids of fairly high

melting-point. The solid alkaloids are, as a rule, insoluble in water, and sparingly so in ether or cold alcohol, but dissolve more readily in hot alcohol or in chloroform. Most alkaloids show the phenomenon of *optical activity*; a few, however, are inactive (atropine, papaverine, piperine, berberine). Of the optically active members, the majority are *lævo*-rotatory, but a few (coniine, narcotine, cinchonine, quinine) possess rotatory power in the opposite sense.

Owing to their therapeutic importance, the detection of alkaloids has received much attention. Qualitatively, they may be recognized by their melting-point, optical rotatory power, and by various distinctive colour tests (notably with sulphuric or nitric acids). Quantitatively, they are usually estimated in the form of one or other of the following insoluble salts: *chloroplatinates* (from chloroplatinic acid, H_2PtCl_6), *chloroaurates* (from $AuCl_3$), *picrates* (from picric acid), *phospho-molybdates*, *periodides* (from a solution of iodine in potassium iodide, KI_3, *Bouchardat's reagent*), or *mercuriodides* (solution of potassium mercuric iodide, K_2HgI_4, *Mayer's reagent*).

The following table affords a summary of a few typical characteristics of the alkaloids :—

Alkaloid.	*Formula.*	*M.p.*	*B.p.*	$[\alpha]_D$	*Colour with H_2SO_4.*	*Periodide.*	*Mercurichloride.*
Piperine	$C_{17}H_{19}O_3N$	128°	—	—	Ruby-red	Steel-blue	White ppt.
Nicotine	$C_{10}H_{14}N_2$	—	247°	+161°	—	Dark blue	Cryst. ppt.
Coniine	$C_8H_{17}N$	—	167°	+18°	—	Large crystals	Pale yellow
Atropine	$C_{17}H_{23}O_3N$	115°	—	—	Pale orange red	Brown ppt.	Yellow (cold) / Red (hot)
Cocaine	$C_{17}H_{21}O_4N$	98°	—	−18°	—	—	—
Ecgonine	$C_9H_{15}O_3N$	205°	—	−57°	—	—	—
Tropine	$C_8H_{15}ON$	62°	233°	—	—	—	White ppt.
Narcotine	$C_{22}H_{23}O_7N$	176°	—	−207°	(Cold) greenish yellow	Brownish-yellow	Small crystals
Narceine	$C_{23}H_{27}O_8N$	170°	—	—	(Hot) dark red-violet	—	M.p. 123°
Papaverine	$C_{20}H_{21}O_4N$	148°	—	—	(Cold) none ; (hot) dark violet	Purple	White needles
Morphine	$C_{17}H_{19}O_3N$	100°	—	−70°	(+FeO) Purple red	Black prisms	—
Codeine	$C_{18}H_{21}O_3N$	150°	—	−136°	(+FeO) Blue	Violet	White needles
Thebaine	$C_{19}H_{21}O_3N$	193°	—	−220°	—	—	—
Hydrastine	$C_{21}H_{21}O_6N$	132°	—	−67°	—	Brown	—
Berberine	$C_{20}H_{17}O_4N$	120°	—	—	—	Clear brown	Yellow
Cinchonine	$C_{19}H_{22}ON_2$	255°	—	−222°	—	Reddish-brown	White ppt.
Cinchonidine	$C_{19}H_{22}ON_2$	201°	—	−108°	—	Pale yellow	Insoluble scales
Quinine	$C_{20}H_{24}O_2N_2$	177°	—	−145°	Pale-blue fluorescence	Greenish	White ppt.
Conchinine	$C_{20}H_{24}O_2N_2$	171°	—	−275°	Blue fluorescence	Golden-yellow	Leaflets
Strychnine	$C_{21}H_{22}O_2N_2$	284°	—	−36°	(+PbO_2) Blue, then violet	Reddish	Insoluble
Brucine	$C_{23}H_{26}O_4N_2$	178°	—	−125°	(+HNO_3) Red	Violet-brown	—

The following are the general features of the chemical behaviour of the alkaloids; from these reactions the general nature of a given alkaloid may frequently be ascertained, as will be gathered from the specific examples cited.

A. Destructive distillation (either alone, or in presence of zinc dust or of lime).

Nicotine yields *pyridine* and *pyrrol*.
Quinine ,, *quinoline*.
Brucine ,, *pyridines*, *indol*, and *skatole*.
Morphine ,, *phenanthrene*.

B. *Hydrolytic agents* (potash, 50 per cent. sulphuric acid, or (occasionally) dilute hydrochloric acid).

Atropine yields *tropine* (base) and *tropic acid*.
Cocaine ,, *ecgonine*, *benzoic acid*, and *methyl alcohol*.
Narcotine ,, *hydrocotarnine* (base) and opianic acid.

C. *Acetylation or benzoylation* (determination of the number of free *hydroxyl* groups).

Number of (OH) groups.
1 in atropine, cinchonine, quinine, codeine.
2 in morphine.

D. *Action of hydriodic acid* (*sp. gr.* 1.8) *at* 130° (determination of the number of *methoxyl* groups).

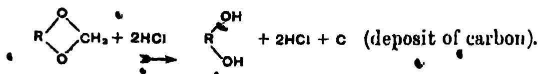
Number of (OCH_3) *groups.*
1 in cocaine, quinine, codeine.
2 in thebaine, brucine, berberine.
3 in narcotine.
4 in papaverine.

E. *Action of concentrated hydrochloric acid* (in sealed tubes at 150°).

(i) *Water* (H_2O) is frequently eliminated:

Tropine, $C_8H_{15}ON$ → Tropidine, $C_8H_{13}N$.
Ecgonine, $C_9H_{15}O_3N$ → Anhydroecgonine, $C_9H_{13}O_2N$.
Morphine, $C_{17}H_{19}O_3N$ → Apomorphine, $C_{17}H_{17}O_2N$,

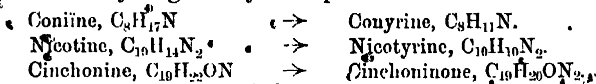
(ii) If the *dioxymethylene* (*piperonyl*) group is present, it is usually decomposed under these conditions:—



The *piperonyl* group is found in papaverine, narcotine, berberine, and other alkaloids.

F. Mild oxidation (hydrogen dioxide, strong sulphuric acid, cold dilute nitric acid, etc.).

(i) Loss of hydrogen may take place:



Coniïne, $C_8H_{17}N$ → Conyrine, $C_8H_{11}N$.
Nicotine, $C_{10}H_{14}N_2$ → Nicotyrine, $C_{10}H_{10}N_2$.
Cinchonine, $C_{19}H_{22}ON$ → Cinchoninone, $C_{19}H_{20}ON_2$.

(ii) Addition of oxygen may occur:



Nicotine, $C_{10}H_{14}N_2$ → Oxynicotine, $C_{10}H_{14}ON_2$.
Strychnine, $C_{21}H_{22}O_2N$ → Strychnonic acid, $C_{21}H_{22}O_3N_2$.

G. Vigorous oxidation (concentrated nitric acid, acid permanganate, etc.).

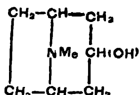
In this case acids of the aromatic and pyridine series are often obtained.

Alkaloid.		*Pyridine acid.*	*Aromatic acid.*
Nicotine	→	Nicotinic	—
Cinchonine	→	Carbocinchomeronic Cinchomeronic Quinolinic	—
Papaverine	→	Carbocinchomeronic	Metahemipinic
Hydrastine	→	Apophyllenic	Opianic

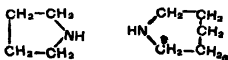
II. The Solanum or Nightshade Alkaloids

A number of alkaloids found in plants of certain genera of the order Solanaceæ, notably in Solanum and Atropa species (nightshade or belladonna), form a closely related group together with cocaine and other bases occurring in the leaves of the cocoa plant. All these substances are simple derivatives of a base

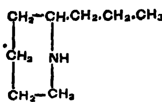
known as *tropine*, which has been proved to possess the constitution



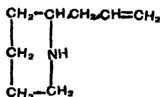
This compound may be regarded as derived from cycloheptamethylene with a "bridged-nitrogen" ring-system inserted, or, perhaps more simply, as a combination of the pyrrolidine and piperidine nuclei :—



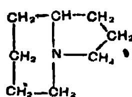
This type of annealed hetero-ring system appears in its simplest form in some of the hemlock alkaloids, derivatives of *coniine*, which we have already seen is α-n-propylpiperidine. Coniine is always accompanied by a number of other alkaloids, the *coniceines*, and it has recently been shown that certain of the latter are piperidine-pyrrolidine or piperidine-trimethyleneimide derivatives. Thus we have—



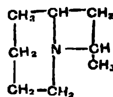
Coniine



α-Coniceine



β-Coniceine



ε-Coniceine

This series illustrates how impossible it is to classify the alkaloids according to the chemical nature of their heterocyclic groups, except in the broadest possible manner.

The tropine alkaloids may be divided into two sub-groups:

(i) *Tropeines* or tropeides of aromatic oxy-acids.

(ii) *Derivatives of tropine carboxylic acid.*

(i) The *tropeines*, which are in general structure comparable to aliphatic esters, include all the belladonna alkaloids, and are distinguished therapeutically by their deadly poisonous nature and their mydriatic action (dilatation of the pupil of the eye).

The chief of these are—

Atropine,	$C\ H\ O_3N$.	Optically inactive. M.p. 115°. Occurs in belladonna. Tropeide of tropic acid.
Hyoscyamine,	,,	*l*-rotatory. M.p. 109°. Occurs in belladonna. Tropeide of tropic acid.
Hyoscine,	,,	Isomeric with the first two. M.p. 55°. Occurs in belladonna. Tropeide of tropic acid.
Apoatropine,	$C_{17}H_{21}O_2N$.	M.p. 62°. A synthetic product. Tropeide of atropic acid.
Homoatropine,	$C\ H_{21}O_3N$.	M.p. 97°. A synthetic product. Tropeide of mandelic acid.

(ii) The *cocaine* alkaloids are derivatives of tropine carboxylic acid, and are very useful local anæsthetics. The best known are—

1-Ecgonine,	$C_9H_{15}O_3N$.	Tropine carboxylic acid. M.p. 205°.
1-Cocaine,	$C_{17}H_{21}O_4N$.	Benzoylecgonine methyl ester. M.p. 98°.
Tropa-cocaine,	$C_{15}H_{19}O_2N$.	Benzoyl-ψ-tropine. M.p. 49°.

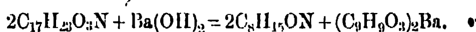
In order to obtain some idea of the structure of these substances, we will consider the following questions in some detail:—

(*A*) The decompositions and synthesis of atropine.

(*B*) The structure of the acids contained in the most common tropeines.

(*C*) The conversion of tropines to cocaines.

(*A*) *The decompositions and synthesis of tropine.*—This base is obtained when a tropeine is digested with baryta solution; in the case of atropine,

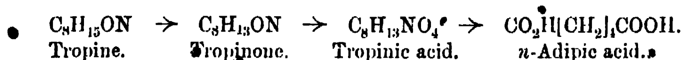


$$2C_{17}H_{23}O_3N + Ba(OH)_2 = 2C_8H_{15}ON + (C_9H_9O_3)_2Ba.$$

Its chief reactions are—

(*a*) Heated with lime, methylamine is evolved, indicating the presence of the *methylimino group* $>N.CH_3$.

(*b*) A ketone, *tropinone*, is formed when tropine is oxidized by chromic acid. By further oxidation an acid, *tropinic acid*, is produced, which on reduction at a high temperature yields *n-adipic acid.*



$$C_8H_{15}ON \rightarrow C_8H_{13}ON \rightarrow C_8H_{13}NO_4 \rightarrow CO_2H[CH_2]_4COOH.$$

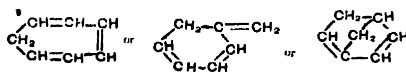
Tropine. Tropinone. Tropinic acid. *n*-Adipic acid.

Hence we may infer the presence of (i) a *secondary alcohol group* - CH(OH) -, and (ii) a chain of the type >CH.CH_2 - CH_2 - CH_2 - CH_2.CH <.

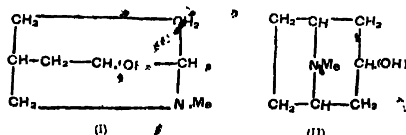
(*c*) Dehydrating agents convert tropine to *tropidine*, which by reduction and distillation of the product with zinc dust yields *a-ethylpyridine* (Ladenburg) :—



(*d*) Exhaustive methylation of tropidine leads finally to the production of a very unsaturated hydrocarbon, *tropilidene*, C_7H_8, which forms a dibromide. This dibromide, on heating at 100°, evolves HBr and produces *benzyl bromide*, $C_6H_5.CH_2Br$ (Merling). The formula of tropilidene might accordingly be



All these facts may be combined in two or three possible formulæ for tropine; the two most probable are those put forward by Merling (I) and by Willstätter (II) :—

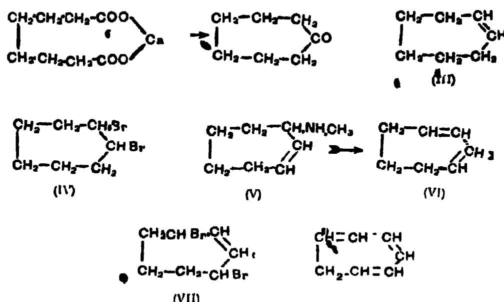


Synthetic evidence confirms the second formula.

The main outlines of the synthesis, which is due to Willstatter, are as follows :—

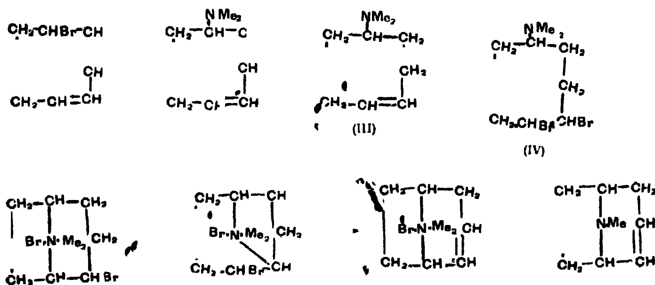
(*a*) *Synthesis of cycloheptatriene.*—Calcium suberate (I) is converted to suberone (II), which by reduction and dehydration gives cycloheptene (III). The dibromide of this (IV) is converted by methylamine to a dimethylamino-cycloheptene (V), which by the exhaustive methylation process is changed to cycloheptadiene (VI). Two atomic proportions of bromine are added to the

latter compound, and the addition product (VII), when distilled with quinoline, yields cycloheptatriene (VIII).



(b) *Conversion of cycloheptatriene to tropidine.*—One molecular proportion of hydrobromic acid is added to cycloheptatriene, forming the monohydrobromide (I) ; this is treated with dimethylamine, when α-methyltropidine (II) is produced, and on reduction passes into α-methyl tropane (III).

The dibromide of this substance (IV) suffers intramolecular rearrangement on heating, and one of the compounds (V) is formed. Hydrobromic acid is eliminated from this, and tropidine methylbromide (VI) remains, which on distillation gives tropidine (VII).

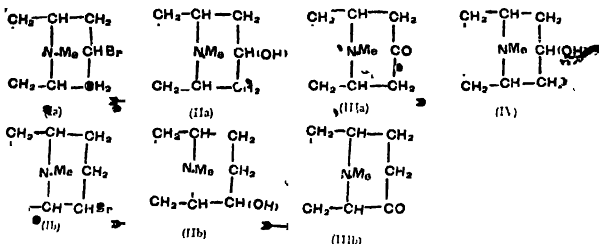


(c) *Conversion of tropidine to tropine.*—When tropidine is warmed with an acetic acid solution of hydrobromic acid, addition of HBr to the double bond in tropidine occurs, and one of the substances Ia or Ib is formed. This is converted to an isomer of tropine by heating with dilute sulphuric acid at 200°. This isomeride is known as ψ-tropine (IIa or IIb).

By oxidation of ψ-tropine the ketone tropinone (IIIa or IIIb) is produced; this is identical with the tropinone formed from natural tropine, and is characterized by forming a di-isonitroso compound and a dibenzaltro-

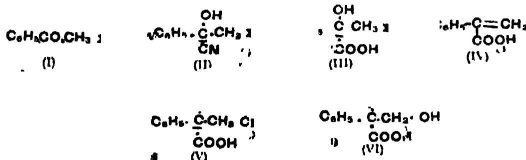
pinone by the Claisen condensation. It, therefore, contains the grouping $-CH_2-CO-CH_2-$, and so must be formulated as IIIa and not IIIb. By reduction of tropinone with zinc dust and acid, tropine itself (IV) is produced.

The isomerism of tropine and ψ-tropine proved puzzling for a time, but it was eventually established that they are geometrical (*cis-trans*) isomerides, and, as in many other cases, one isomer is more stable than the other. In this case ψ-tropine is the *stable* and tropine the labile form ; in accordance with the general rule that in any reaction the less stable form tends to separate first, *tropine* itself therefore results by reduction of tropinone under the mild conditions described. In the former case, however, the temperature of reaction (200°) ensures the conversion of the product to the stable ψ-tropine.



(*B*) *The structure of the acids in the tropeines, atropine and apoatropine.*—It has been stated that these alkaloids contain, in combination with *tropine*, *tropic* and *atropic* acids respectively. These two acids have been synthesized from acetophenone (I) as follows :—

Acetophenone cyanhydrin (II), when treated with cold concentrated hydrochloric acid, is hydrolysed to α-phenyllactic or atrolactinic acid (III) ; if the latter is boiled with the same reagent, water is eliminated and α-phenylacrylic or atropic acid (IV) results. Addition of anhydrous hydrogen chloride to atropic acid produces β-chloro-α-phenylpropionic acid (V), which passes into tropic acid (α-phenylhydracrylic acid VI) on boiling with aqueous alkali carbonates :



Tropic acid may be resolved into its optically active forms by fractional crystallization of the quinine salts.

From either tropic, atropic, atrolactinic, or mandelic acids, the tropeines may be produced by the following methods :—

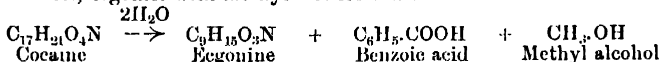
(*a*) Esterification in the usual way by heating tropine and one of the acids with 3 per cent. of anhydrous HCl.

(*b*) Acetylation of the acid, conversion of the acetyl-acid so produced to its chloride, and condensation of the latter with tropine hydrochloride. The resulting acetyltropeine is saponified by allowing it to remain in contact with water for some time. This method leads to a much better yield of the tropeine than the former.

(*C*) *The conversion of tropines to cocaines.*—When tropine is oxidized to tropinone, and the sodium salt of the latter (I) is suspended in ether and saturated with a stream of carbon dioxide, a mixture of the sodium salts of two carboxylic acids is formed (IIa, b), since the sodium tropinone reacts partly in the ketonic (Ia), and partly in the enolic (Ib), form.

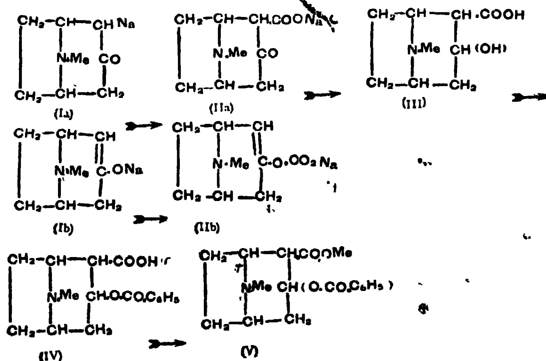
The ketonic isomer is produced in least amount, but when this is reduced, a *tropine carboxylic acid* (III) results which proves to be racemic *ecgonine*.

Now *l*-ecgonine is produced when ordinary *l-cocaine* is digested with dilute baryta water, together with methyl alcohol and benzoic acid :

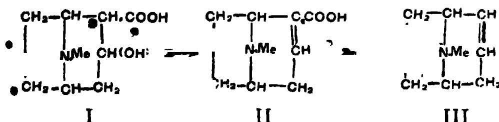


$$\underset{\text{Cocaine}}{C_{17}H_{21}O_4N} \xrightarrow{2H_2O} \underset{\text{Ecgonine}}{C_9H_{15}O_3N} + \underset{\text{Benzoic acid}}{C_6H_5.COOH} + \underset{\text{Methyl alcohol}}{CH_3.OH}$$

Consequently cocaine (V) appears to be the methyl ester of benzoyl-*l*-tropine carboxylic acid, and this has been proved by benzoylating ecgonine, and esterifying the benzoylecgonine (IV) with methyl alcohol :

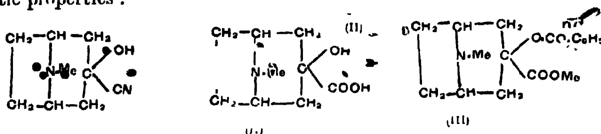


As might be foreseen from this synthetic evidence, ecgonine can be transformed to tropidine. When boiled with phosphorus oxychloride, ecgonine (I) passes into anhydroecgonine (II), which loses carbon dioxide on heating under pressure with hydrochloric acid, forming tropidine (III).

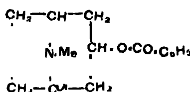


Again, by means of the cyanhydrin of tropinone (I), a-tropine carboxylic acid (II), isomeric with ecgonine, may be synthesized.

By benzoylation and esterification this gives rise to a-cocaine (III), isomeric with ordinary cocaine, but not occurring in nature, and possessing no anesthetic properties :



Finally *tropa-cocaine*, which sometimes accompanies cocaine in the cocoa plant, is the benzoyl derivative of ψ-tropine, since hydrolytic agents break it down into that substance and benzoic acid :



III. The Opium or Poppy Alkaloids

Most members of the poppy family are tolerably rich in alkaloids, but the opium poppy (*Papaver somniferum*) is especially noteworthy in this respect, and the milk-like juice from the unripe seed heads of this species constitutes the drug *opium* when dried.

The therapeutically interesting compounds present in opium may be divided into three classes :

(a) *Non-nitrogenous substances.* About 4 per cent. Meconic acid, meconine, etc.

(b) *Iso-quinoline alkaloids.* About 6 per cent. Narcotine, papaverine, etc.

(c) *Oxazine alkaloids.* About 10 per cent. Morphine, etc.

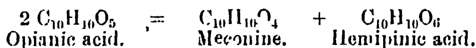
(*a*) *Non-nitrogenous Substances.*—Although these are, strictly speaking, not alkaloids, we will review their structure because they are frequently found as decomposition products of the isoquinoline alkaloids, as well as accompanying the true alkaloids in poppy-juice.

Meconic acid, $C_7H_4O_8$, $3H_2O$, occurs as morphine salt in opium, and has been shown (compare chap. vi., p. 85) to be a dioxy-γ-pyrone dicarboxylic acid of the formula :

Meconine, $C_{10}H_{10}O_4$, melting at 102°, is, on the other hand, a *benzo-lactone* or *phthalide* (chap. iii., p. 51). It is derived from meconinic acid, $C_{10}H_{12}O_5$, which exists, however, only in the form of metallic salts, which revert to meconine when acidified.

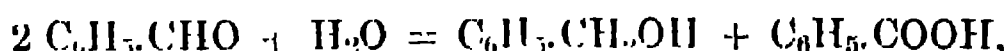
Meconine itself is of importance owing to its formation from narcotine (p. 147) on boiling the latter alkaloid with water ; at the same time a closely related compound, *opianic acid*, $C_{10}H_{10}O_5$, is also produced.

Opianic acid is changed to sodium meconinate by the action of sodium amalgam, and on acidifying the product meconine is obtained ; again, when heated with strong aqueous potash, opianic acid furnishes a mixture of meconine and hemipinic acid :



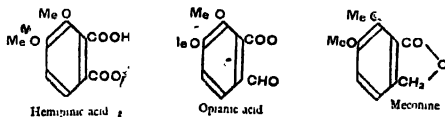
$$\underset{\text{Opianic acid.}}{2\,C_{10}H_{10}O_5} = \underset{\text{Meconine.}}{C_{10}H_{10}O_4} + \underset{\text{Hemipinic acid.}}{C_{10}H_{10}O_6}$$

This reaction is analogous to the decomposition of benzaldehyde by caustic alkali :



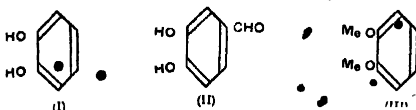
$$2\,C_6H_5.CHO + H_2O = C_6H_5.CH_2OH + C_6H_5.COOH,$$

and so, since hemipinic acid is known to have the structure given below, it is reasonable to suppose that the structures of opianic acid and meconine are somewhat as follows :—



The precise orientation of the carboxyl and aldehyde groups in opianic acid is finally established by the fact that on distillation with soda-lime it yields *vanillin methyl ether* (III), which may be synthetically prepared from

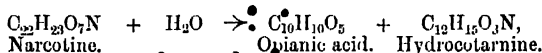
pyrocatechol (I) by Reimer's reaction, the product, protocatechuicaldehyde (II) being then methylated :



(*b*) *Isoquinoline Alkaloids.*—The chief members of this group, and the only ones which we shall consider, are *narcotine*, *narceine*, and *papaverine*. Each of these, by the action of violent chemical reagents, such as heated zinc dust or fused potash, gives rise to simple derivatives of isoquinoline; none of them possess very marked physiological properties.

Narcotine, $C_{22}H_{23}O_7N$, melting at 176°, is the most abundant of the three, and forms sometimes as much as 6 per cent. of the dried juice of the poppy. It is a very complicated alkaloid, and its structure has only recently been placed beyond doubt; at the present time, however, the synthetic evidence (which is usually necessary to decide the precise constitution of these complex bodies) has been supplied almost completely, although there still remain a few missing links in the chain.

Narcotine, when heated with water at 140°, gives a mixture of *opianic acid* and a substance, *hydrocotarnine*,



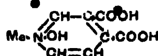
$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2O \rightarrow \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N},$$

whilst by gentle reduction, *meconine* and *hydrocotarnine* are produced.

The latter compound is oxidized by mild reagents (such as hydrogen dioxide) to *cotarnine*, $C_{12}H_{15}O_4N$; and since the formula for narcotine depends on the structure of cotarnine, we must discuss in a few words the nature of this product.

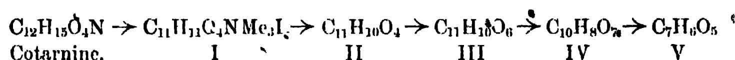
The chief decompositions of *cotarnine* are :

(i) Nitric acid oxidation produces *apophyllenic acid*,

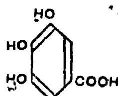


(ii) Methylation gives rise to cotarnomethine methyl iodide (I), which,

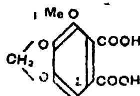
when heated with alkali, yields trimethylamine and cotarnone (II). Oxidation of cotarnone leads to a lactone (III), and then to cotarnic acid (IV), which, when reduced in sealed tubes with phosphorus and hydriodic acid, gives gallic acid (V):



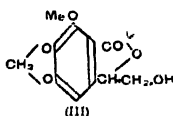
Now, cotarnic acid is dibasic and readily forms an anhydride; moreover, it contains a methoxyl and a methylene-ether group. Hence, since gallic acid is

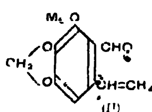


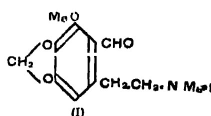
cotarnic acid is most probably



and working back from this, we arrive at the constitutions of the intermediate products I-III:



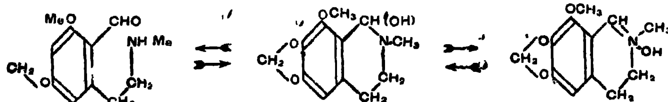




so that, finally, *cotarnine* must be



This might conceivably be a kind of tautomeric substance, and react either as an aromatic alphylamine or a reduced isoquinoline:



It has been shown spectroscopically by Dobbie and co-workers that some such change does occur, one form or the other predominating according to the solvent and other external conditions; and this hypothesis also renders explicable the formation of the pyridino-betaine-like *apophyllenic acid.*

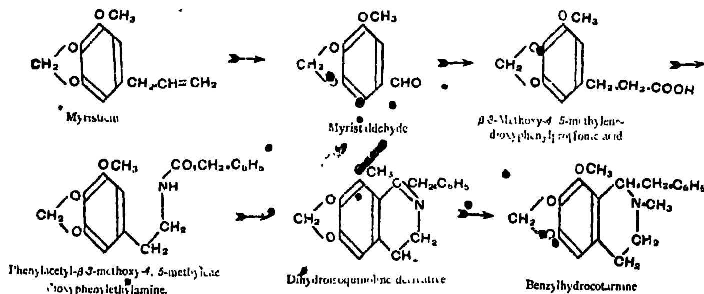
We will now summarize a recent synthesis of cotarnine by Salway (1910):—

Commencing with myristicin (which had been synthesized previously), the allyl group present was isomerized to the propenyl radicle by hot alkali, and oxidation of the product produced *myristaldehyde*, which was condensed with ethyl acetate by means of sodium ethoxide, when hydrolysis and alkaline reduction produced *β-3-methoxy-4.5-methylenedioxyphenylpropionic* acid.

The amide of this acid was treated with potassium hypobromite, and the resulting amine heated with the chloride of phenylacetic acid, when *phenyl-acetyl-β-3-methoxy-4.5-methylenedioxyphenylethylamine* was obtained.

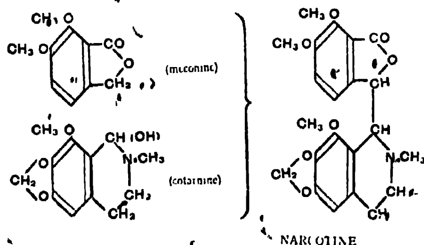
On heating this with phosphoric anhydride in boiling xylene the carbonyl group present (or rather its enolic form) condensed with the benzenoid nucleus in both of the *ortho*-positions to the ethylamine radicle, so that two isomeric dihydroisoquinoline derivatives were produced.

One of these, possessing the formula below (as proved by the preceding analytical evidence), yielded a methylchloride, which, when reduced, gave *benzylhydrocotarnine*, and the latter compound yielded *cotarnine* on oxidation with manganese dioxide and dilute sulphuric acid:

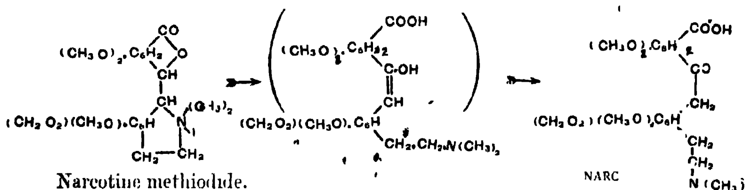


A little later Perkin and Robinson (1911) showed that *cotarnine* condenses with *meconine* in boiling alcoholic solution and forms *gnoscopine*, an alkaloid isomeric with *narcotine*, and, indeed, its racemic form. Gnoscopine is converted to the optically active narcotines by fractional crystallization of its *d*-bromo-camphorsulphonate, and is also formed by boiling natural narcotine with alcohol, when racemization sets in.

The constitution of *narcotine* itself is thus definitely shown to be:



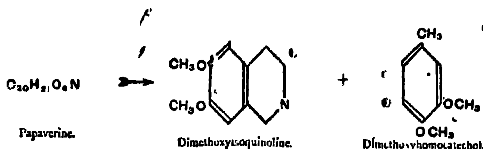
Narceine, $C_{23}H_{27}O_8N$, which accompanies narcotine in opium to a small extent, was known much earlier (1890) to be closely related to the latter alkaloid. It is produced, in fact, according to the following scheme when narcotine methiodide is distilled with alkali:



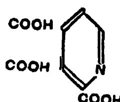
Narcotine methiodide.

Papaverine, $C_{20}H_{21}O_4N$, is shown by the Zeisel method to contain four methoyxl groups, so that all the oxygen atoms are combined as $-O-CH_3$

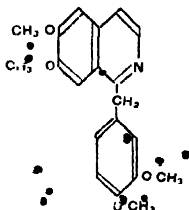
When fused with alkali, an *isoquinoline* and a *homo-catechol* derivative are produced; the structure of the products is as follows:-


Papaverine. Dimethoxyisoquinoline. Dimethoxyhomocatechol

Oxidation with potassium permanganate decomposes papaverine into *a-carbocinchomeronic acid*,



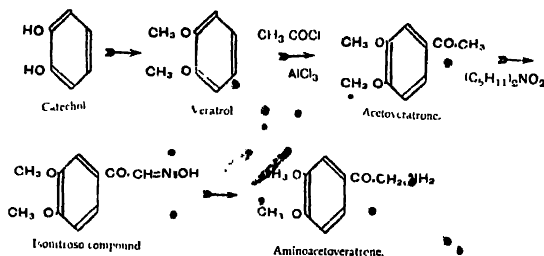
Mainly from these data it was believed that papaverine possessed the structure



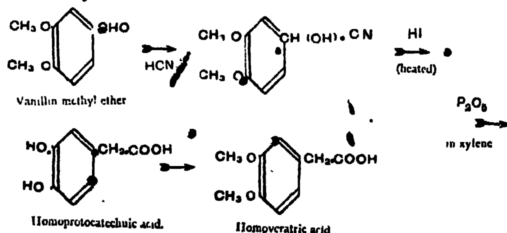
and this constitution has been recently confirmed by a somewhat complicatated synthesis, due to Pictet (1909).

The following is a diagrammatic outline of this synthesis :—

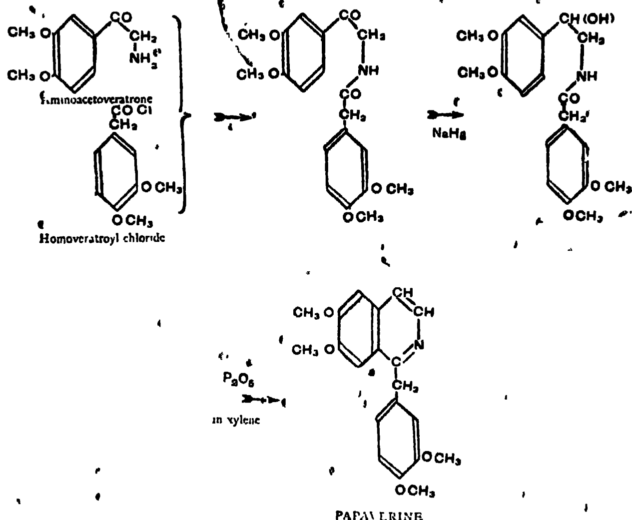
(i) *Synthesis of aminoacetoveratrone.*



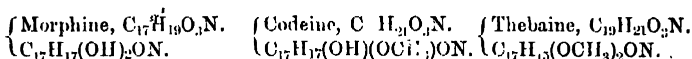
(ii) *Synthesis of homoveratric acid.*



(iii) *Combination of these compounds.*



(*c*) *Oxazine Alkaloids.*—These are *morphine*, *codeine*, and *thebaine*, and are the poisonous hypnotic constituents of opium. They differ from most alkaloids in containing no pyridine or pyrrol residues, but include, on the other hand, the *oxazine* (chap. IX., p. 176) and *phenanthrene* ring systems. They are tertiary bases of a closely related nature, differing in their degree of methylation:


Morphine, $C_{17}H_{19}O_3N$. $C_{17}H_{17}(OH)_2ON$.
Codeine, $C\ H_{21}O_3N$. $C_{17}H_{17}(OH)(OCH_3)ON$.
Thebaine, $C_{19}H_{21}O_3N$. $C_{17}H_{15}(OCH_3)_2ON$.

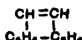
The following summary indicates the chief points of our at present imperfect knowledge of the constitution of this group :

(*a*) *Morphine*, which by methylation with diazomethane gives *codeine*, is a weak base and at the same time a dihydric phenol.

Since it is excessively easily oxidized, and, on the other hand, *protocatechuic acid* C_6H_3—OH (1), OH (2), COOH (4) is obtained from it by fusion with potash, it is

reasonable to suppose that the phenolic groups are in the *ortho* position to each other.

(*b*) Vongerichten and Schrötter showed in 1881 that the morphine alkaloids, when distilled with zinc dust, gave *phenanthrene*, but no pyridine derivatives :



(*c*) Vongerichten and Knorr found that *codeine methiodide* (I), when heated under pressure with concentrated hydrochloric acid, was converted into a mixture of two substances, one of the formula $C_4H_{11}ON$ (III), and the other a dihydric phenol, *morphol* (IV).

(*d*) On the other hand, Knorr showed that *codeine methiodide* is transformed by boiling with aqueous potash into a series of isomeric bases, the *methylmorphimethines* (II). Methylmorphimethine, treated as before with strong hydrochloric acid, gives *morphol* (IV) and the substance $C_4H_{11}ON$ (III).

(*e*) *Morphol*, $C_{14}H_{10}O_2$, gives *phenanthrene* on distillation with zinc dust, and a mixture of *phthalic* and *protocatechuic acids* on oxidation with permanganate. It is therefore probably a dioxyphenanthrene of formula IV.

(*f*) The substance, $C_4H_{11}ON$ (III), by addition of methyl iodide, forms *choline iodide* (V), and is possibly *oxyethyldimethylamine* (VI). Such a compound by intramolecular rearrangement and simultaneous oxidation could give rise to the reduced *oxazine* or *morpholine* (VII) (*cf.* chap. ix., p. 177).

(*g*) *Methylmorphimethine*, boiled with acetic anhydride, has been shown by Knorr to yield *acetoxymethoxyphenanthrene* (VIII) and *acetoxyethyldimethylamine* (IX).

(*h*) *Morphol* has been synthesized by Pschorr from *nitrovanillin* (X), which by condensation with phenylacetic acid (Perkin's reaction) yields the acid XI, and this by reduction, diazotization, and distillation of the diazonium hydrate yields *dimethyl morphol* (XII), which is converted by hydriodic acid to *morphol* (IV).

These reactions are represented on the next page :

$C_{18}H_{21}O_3N(CH_3)I$ (I)

KOH →

$C_{18}H_{20}O_3N(CH_3)$ (II)

$(CH_3CO)_2O$ →

$C_{14}H_8(OCH_3)(O.CO.CH_3)$ (VIII) + $CH_3.CO.O.CH_2CH_2N(CH_3)_2$ (IX)

conc HCl →

$C_4H_{11}ON$ (III) + (IV)

CH_3I →

$CH_2OH-CH_2N(CH_3)_3I$ (V)

$CH_2.OH-CH_2N(CH_3)_2$ (VI) → (VII) $O(CH_2CH_2)_2NH$

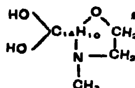
(IV) 3,4-dihydroxyphenanthrene: HO, HO, CH=CH

← (XII) 3,4-dimethoxyphenanthrene: CH_3O, CH_3O, CH=CH

← (XI) CH_3O, CH_3O, NO_2-substituted C_6H_2–CH=C(COOH)–C_6H_5

← (X) CH_3O, CH_3O, NO_2-substituted C_6H_2–CHO + $CH_2(C_6H_5)COOH$

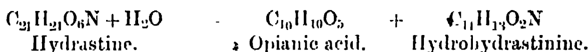
No further synthetic evidence has yet been obtained, however, with regard to the mode of union of the phenanthrene and oxazine nuclei, and it can only be said that morphine is a substance of the composition



IV. The Barberry Alkaloids

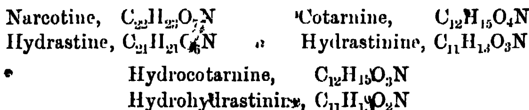
We will next consider some alkaloids, closely related in structure to narcotine, which occur in some plants of the order Ranunculaceæ. The chief of these are *hydrastine* (found in the English barberry and some allied North American genera) and *berberine*, which also occurs in the barberry shrub.

Hydrastine, $C_{21}H_{21}O_6N$, a basic substance melting at 132°, resembles narcotine in the first place in its behaviour with hydrolytic agents, when opianic acid and a compound *hydrohydrastinine* result:



$$\underset{\text{Hydrastine.}}{C_{21}H_{21}O_6N + H_2O} = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrohydrastinine.}}{C_{11}H_{13}O_2N}$$

By mild oxidation *hydrohydrastinine* becomes *hydrastinine*, $C_{11}H_{13}O_3N$, which resembles *cotarnine* very closely. If we now compare the formulæ for narcotine, cotarnine, and hydrocotarnine with those of hydrastine, hydrastinine, and hydrohydrastinine, we see that the hydrastine derivatives contain a methoxyl group less than the corresponding narcotine compounds:



Narcotine,	$C_{22}H_{23}O_7N$	Cotarnine,	$C_{12}H_{15}O_4N$
Hydrastine,	$C_{21}H_{21}O_6N$	Hydrastinine,	$C_{11}H_{13}O_3N$
		Hydrocotarnine,	$C_{12}H_{15}O_3N$
		Hydrohydrastinine,	$C_{11}H_{13}O_2N$

The further study of the reactions of hydrastinine shows that these alkaloids possess structures parallel in all respects to

those of the narcotine group, except that they contain one less methoxyl radicle.

(*a*) *Isoquinoline* is produced when hydrastinine is distilled with zinc dust.

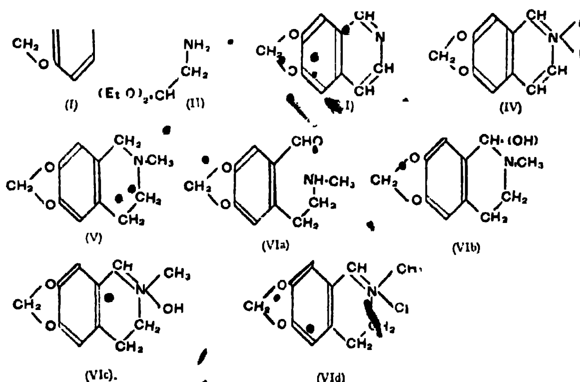
(*b*) Hydrastinine, like cotarnine, contains both a basic and an aldehydic group.

(*c*) *Apophyllenic acid* is formed when hydrastinine is oxidized with nitric acid.

The synthesis of hydrastinine by Fritsch in 1895 proved that this compound only differed, indeed, from cotarnine, structurally as well as empirically, by the absence of the methoxyl radicle, $-OCH_3$, which is found in the latter compound.

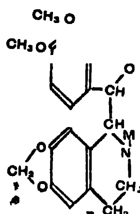
The operation proceeds first of all by a general method of isoquinoline-ring synthesis already mentioned in chap. vii. (p. 114):

Piperonal (I) and *aminoacetal* (II) yield a condensation-product which, in presence of concentrated sulphuric acid, loses two molecules of alcohol and forms *methylene-dioxyisoquinoline* (III). Reduction of the *methiodide* of this base (IV) leads to the production of *hydrohydrastinine* (V), which may be oxidized to *hydrastinine* (VI a, b, c, d). The latter substance, like cotarnine (p. 148), behaves under varying conditions as (*a*) an aldehyde, (*b*) a carbinol base, or (*c*) an ammonium base; its salts (*d*) also belong to the ammonium type.

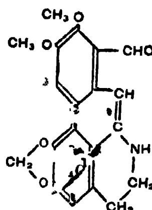


Hence, since the alkaloid itself, *hydrastine*, breaks down into opianic acid and hydrastinine, just as narcotine yields opianic

acid and cotarnine, it is reasonable to suppose that the remainder of the hydrastinine molecule is perfectly analogous to that of narcotine, so that its formula becomes:



The other alkaloid which is found in barberries, *berberine*, has not yet been synthesized, but by means of its decomposition products a formula has been evolved for it by Perkin (1910), according to which this substance resembles hydrastine and narcotine in the isoquinoline half of its molecule; moreover, the mode of union of the rest of the molecule with the first-mentioned part is very similar to that in either of the other two alkaloids. The proposed formula is as follows:—



V. The Cinchona Alkaloids

The next group of the alkaloids which must be considered are usually known as the quinoline alkaloids, since by zinc dust distillation they yield quinoline and its simple derivatives.

The compounds in question occur chiefly in different varieties of cinchona bark, and instead of possessing poisonous qualities in common with most alkaloids, they are exceedingly valuable drugs (quinine). As we shall see shortly, however, a very

simple intramolecular rearrangement converts each of the cinchona alkaloids into violent poisons.

Although known to the Indians and Spaniards some centuries ago as an excellent medicine, cinchona bark was not minutely studied until about 1820 (Pelletier and Caventou). It has since been found to contain, in addition to certain aromatic acids (especially *tannic acid*, $C_{14}H_{14}O_{10}$, and the optically active *quinic acid*, $C_6H_7(OH)_4.COOH$), the following four alkaloids :—

Cinchonine, $C_{19}H_{22}ON_2$. Cinchonidine, $C_{19}H_{22}ON_2$.
Quinine, $C_{20}H_{24}O_2N_2$. Conchinine (Quinidine), $C_{20}H_{24}O_2N_2$.

It is best to consider the structure of these bases in the following order :—

A. *General reactions of all four bases.*

B. *The structure of cinchonine.*

C. *The structure of quinine.*

D. *The relation of cinchonidine to cinchonine, and of conchinine to quinine.*

A. *General Reactions.*—The following reactions are characteristic of each of the four alkaloids :

(*a*) When distilled with zinc dust, quinoline is formed.

(*b*) Each forms a dimethiodide.

(*c*) Each yields a monoacetyl and a monobenzoyl derivative.

(*d*) (i) These alkaloids can each absorb one molecular proportion of bromine or of halogen acid.

(ii) By oxidation with cold permanganate, formic acid, and an acid containing one carbon atom less than the original alkaloid, is produced.

Hence we may at once make the following deductions :—

(*a*) These alkaloids contain a *quinoline* nucleus.

(*b*) They contain two *tertiary nitrogen atoms.*

(*c*) They possess one alcoholic or phenolic *hydroxyl* group.

(*d*) They also contain the *vinyl* radicle $-CH:CH_2$.

Two further general reactions may also be mentioned :

(*e*) By gentle oxidation with chromic acid, *ketones* of the same carbon content as the original alkaloids result; cinchonine and cinchonidine both furnish the same ketone, *cinchoninone*, and similarly, quinine and conchinine both yield the isomeric *quininone* (Rabe).

(*f*) When heated with dilute acetic acid, isomeric bases are produced, evidently by intramolecular rearrangement; the new bases (*cinchotoxines*) are violent poisons, and instead of possessing two tertiary nitrogen atoms and a hydroxyl group, are now found to contain one *tertiary* and one *secondary* (*imino*) nitrogen atom and a carbonyl group (von Miller and Rohde).

We may accordingly conclude:

(*e*) That all four bases are exceedingly closely related, and that in all four there is a secondary alcohol radicle $>CH(OH)$.

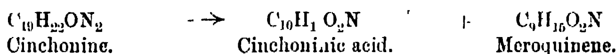
(*f*) That a group of the nature $>C(OH)-N<$ in the original alkaloids has been broken down by isomerization into the radicles $>C:O$ and $HN<$.

B. *The Structure of Cinchonine.*—We may now proceed to discuss the more precise nature of these bases, and this may be done most profitably by confining ourselves for the moment to one of them—*cinchonine.*

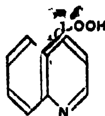
We must, however, look to some further decompositions of cinchonine before we can make any definite conclusions. The chief of these are:

(*a*) *Oxidation.*

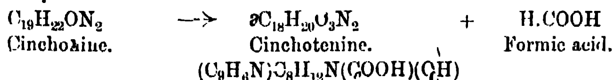
(i) *By chromic acid in presence of sulphuric acid* (Konigs). This produces *cinchoninic acid* (quinoline γ-carboxylic acid, p. 113), and a base *meroquinene*:



$C_{19}H_{22}ON_2$	→	$C_{10}H_7O_2N$	+	$C_9H_{15}O_2N$
Cinchonine.		Cinchoninic acid.		Meroquinene.



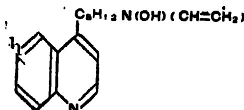
(ii) *By potassium permanganate* (Königs). In this instance, *formic* acid and a compound *cinchotenine* (containing a *hydroxyl* and a *carboxyl* group) result. By further oxidation *cinchotenine* yields cinchoninic acid, so that it must still contain the quinoline nucleus of cinchonine:



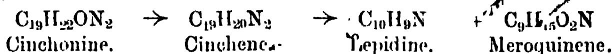
$C_{19}H_{22}ON_2$	→	$C_{18}H_{20}O_3N_2$	+	H.COOH
Cinchonine.		Cinchotenine.		Formic acid.
		$(C_9H_6N)C_8H_{12}N(COOH)(OH)$		

Moreover, since *cinchotenine*, in contradistinction to cinchonine, cannot take up a molecular proportion of halogen acid, it is plain that the *vinyl* group present in cinchonine has been oxidized to formic acid.

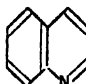
Hence we may write cinchonine as—



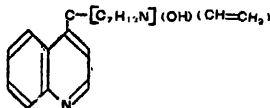
(*b*) *Dehydration* of cinchonine by means of phosphorus pentachloride removes a molecule of water and produces *cinchene*, which, by treatment with not too concentrated aqueous phosphoric acid, absorbs two molecules of water, and is broken down into lepidine (γ-*methyl-quinoline*) and *meroquinene* (see above):



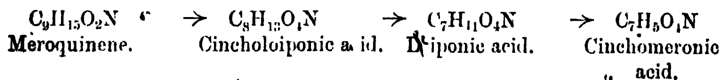
$C_{19}H_{22}ON_2$	→	$C_{19}H_{20}N_2$	→	$C_{10}H_9N$	+	$C_9H_{15}O_2N$
Cinchonine.		Cinchene.		Lepidine.		Meroquinene.



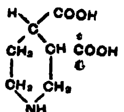
Taking this in conjunction with the formation of cinchoninic acid and meroquinene from cinchonine by oxidation, it is plain that the quinoline nucleus must be united to the meroquinene part of the molecule through a carbon atom attached to the γ-quinoline carbon atom, so that we may further formulate chinchonine as:



(*c*) *Meroquinene*, in which, by the way, the *vinyl group* $-CH:CH_2$ still persists, is oxidized by acid permanganate solution at 0° to *cincholoiponic acid*, which by the same reagent at higher temperatures yields *loiponic acid*. The latter acid, when warmed with concentrated sulphuric acid, gives *cinchomeronic acid*, and by analogy with the similar oxidation of piperidine to pyridine, is a *hexahydrocinchomeronic acid*.



$C_9H_{15}O_2N$	→	$C_8H_{13}O_4N$	→	$C_7H_{11}O_4N$	→	$C_7H_5O_4N$
Meroquinene.		Cincholoiponic acid.		Loiponic acid.		Cinchomeronic acid.

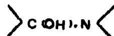




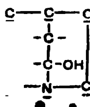
So much was known by about 1897; the work up till then had been carried on mainly by two German chemists, Königs and von Miller. These agreed readily as to the constitution of *loiponic acid*, but a difference of opinion was manifested as to the manner of insertion of the extra methylene ($-CH_2-$) grouping present in *cincholoiponic acid*, Königs regarding it as a *substituted acetic acid*, whilst von Miller and Röhde considered it to be a *methyl homologue of loiponic acid.*

The different structures thus appearing may be best represented together a little later, and before giving them we will discuss the evidence for the position of the hydroxyl group in the cinchonine molecule.

As already mentioned, von Miller and Rohde showed (in 1894) that cinchonine may be isomerized into an iminoketone, *cincholoxine*, and concluded that the non-quinolinic *tertiary nitrogen* atom of cinchonine was adjacent to the alcoholic *hydroxyl* radicle:



This was accounted for by assuming that across the piperidine nucleus (of meroquinene) there existed (in cinchonine) a "bridged-ring" system of the general type:



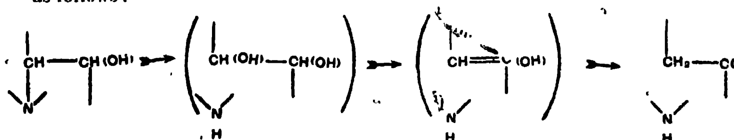
Now, whatever formula be adopted for *meroquinene*, it is certain that the quinoline residue in cinchonine must be united to the *hydroxylic* carbon atom therein (for otherwise the known decompositions of cinchonine and meroquinene could not be explained). Consequently this hydroxylic carbon atom must be *tertiary, i.e.* possesses no hydrogen atom attached to it.

On the other hand, Rabe has recently shown (1908) that cinchonine may be oxidized to a ketone, *cinchoninone*, with the same number of carbon atoms, and only differing from cinchonine by the loss of two hydrogen atoms (*cf. A* (a), p. 158); this proves beyond doubt that the *alcoholic radicle* is of a *secondary*, and not a tertiary, nature, and so this worker has modified the conception of the cinchonine formula as shown below.

We can now illustrate the views of these three scientists by developing their respective formulæ for cinchonine from that of loiponic acid :

	Königs.	*von Miller.*	*Rabe.*
Loiponic acid.	COOH CH COOH.CH CH₂ CH₂ CH₂ NH	Same	Same
Cincholoiponic acid.	CH₂.COOH CH COOH.CH CH₂ CH₂ CH₂ NH	CH₃ COOH C COOH.CH CH₂ CH₂ CH₂ NH	Same as Königs
Meroquinene.	CH₂.COOH CH CH₂=CH.CH CH₂ CH₂ CH₂ NH	CH₃ COOH C CH₂=CH.CH CH₂ CH₂ CH₂ NH	Same as Königs
Cinchonine.	CH₂=CH.CH—CH—CH₂ CH₂ HO.C CH₂—N—CH₂ CH₂ N	CH₃ CH₂=CH.CH—C—CH₂ HO.C CH₂—N—CH₂ CH₂ N	(1) (2) CH₂=CH.CH—CH—CH₂ CH₂ (3) CH CH₂—N—CH₂ (4) CHOH N

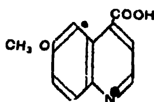
It will be observed that Rabe's formula, whilst accounting for the formation of cinchoninone, does not interfere with the production of an iminoketone by intramolecular rearrangement, the transformation presumably taking place as follows :—



C. *The Structure of Quinine.*—When quinine is oxidized by chromic acid and sulphuric acid, an equimolecular mixture of meroquinene and an acid, $C_{11}H_9O_3N$ (*quininic acid*), is formed.

Again, quinine ($C_{20}H_{24}O_2N_2$) contains the atoms CH_2O more than cinchonine ($C_{19}H_{22}ON_2$), and, moreover, quinine is found by Zeisel's method to contain one methoxyl group, whereas cinchonine possesses none. Hence it is obvious that a hydrogen atom in cinchonine is replaced by methoxyl (OCH_3) in quinine.

The oxidation experiment shows that this extra radicle is present in the quinoline nucleus, and, as a matter of fact, *quininic acid* has been synthetically shown to be *p-methoxyquinoline-γ-carboxylic acid*:



Accordingly, the formula of quinine is known at once, if that of cinchonine be assumed.

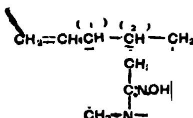
It may be remarked here that there is at present but little synthetic evidence of the constitution of this group of the alkaloids.

D. *The Relation of Cinchonidine to Cinchonine, and of Conchinine (Quinidine) to Quinine.*—There remain the respective isomers of cinchonine and of quinine. These have been supposed for many years to be stereoisomerides, and Rabe has recently proved the truth of this contention (191?). All four bases are of course optically active, but in varying degree; now, if Rabe's formula for cinchonine (p. 162) be examined, it will be seen that the carbon atoms numbered 1, 2, 3, and 4 are all asymmetric.

It will be remembered that *cinchonine* and *cinchonidine* both yield one and the same *cinchoninone* by oxidation, and *cinchotoxine* by isomerization. Cinchoninone has been proved to exist partly in the enolic form, so that here, as well as in cinchotoxine, the asymmetry of the carbon atoms 3 and 4 is destroyed. Hence the difference between cinchonine and cinchonidine lies in the different spacial configurations of the groups about the atoms 3 and 4, those about 1 and 2 being the same in each alkaloid.

Similarly, since *quinine* and *conchinine* give the same *quininone* and *quinotoxine*, the isomerism of these two alkaloids is also due to the configuration about the corresponding asymmetric atoms 3 and 4.

Further still, it has been found that both *cinchoninone* and *quininone*, when acted on by amyl nitrite, give a substance of the structure



and, whether cinchonine, cinchonidine, quinine, or quinidine is used as starting material, the resulting product is optically the same in each case. Consequently the same asymmetrical configuration persists throughout the four members of these naturally occurring substances, so far as the atoms above numbered 1 and 2 are concerned.

VI. The Nux Vomica Alkaloids

The seeds of various species of *Strychnos* (*nux vomica*) have long been known to contain some very poisonous alkaloids. The chief of these, *strychnine* and *brucine*, were definitely isolated by Pelletier and Caventou at about the same period as quinine (1819), but their structure is still unknown.

Both are quite strong bases, and react alkaline to litmus; they are lævorotatory, and exert the same paralytic kind of toxic effect, strychnine being more powerful in this respect.

The few definite facts known as to their decompositions are as follows:—

(*a*) *Strychnine* has the empirical formula, $C_{21}H_{22}O_2N_2$, and *brucine*, $C_{23}H_{26}O_4N_2$.

(*b*) Brucine contains two methoxyl groups, and strychnine none at all. Since their difference in empirical composition is $C_2H_4O_2$, and from their exceedingly close similarity in general properties, it is very probable that *brucine* is a *dimethoxystrychnine*.

(*c*) Distilled with zinc dust, both alkaloids yield indole, skatole, and various pyridines.

(*d*) Both alkaloids can take up a molecular proportion of bromine, indicating the presence of a "double bond."

(*e*) Various complicated reactions lead to the production of the following substances:—

Strychnic acid.—An iminocarboxylic acid, indicating the grouping, > *N.CO*·.

Nitro-, and *sulphonation* products, indicating the presence of a *benzenoid residue*.

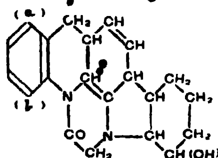
Methylstrychnine.—Analogous to a *quinoline betaine.*

An *acid*, $C_{15}H_{17}O_2N_2.COOH$, which gives *carbazole* when heated with zinc dust.

A *ketonic acid*, *strychninonic acid*, $C_{21}H_{20}O_6N_2$, of the same carbon content as strychnine, so that strychnine probably contains the group *-CH(OH)-*.

Brucine can be converted into a derivative (still containing two methoxyl groups) which by oxidation loses both of these and forms a *para*-quinone, so that the (CH_3O) radicles doubtless occupy *para*-positions to each other in a benzene ring.

Perkin has combined all these facts into a structural formula, which, whilst at present unsupported by direct experimental evidence, gives a good representation of the chemical behaviour of these alkaloids; the formula below is that assigned to *strychnine*, that for *brucine* differing only by the presence of two methoxy-groups in position (*a*) and (*b*):



CHAPTER IX

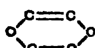
SIX-MEMBERED POLYHETEROATOMIC RING-SYSTEMS: THE AZINES AND ALLIED COMPOUNDS

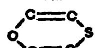
I. General

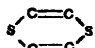
At the close of our study of the furfurane, thiophene, and pyrrol series, it was necessary to add a chapter showing how, by replacement of methine (CH) groups in these substances by oxygen, sulphur, or imino-nitrogen, other heterocyclic systems were produced.

We have now to apply the same principle to the pyrones, thiopyrones, and pyridines discussed in chaps. vi. and vii.; the groups to which we need pay more particular attention may be classified as follows:—

Compounds containing two oxygen or sulphur atoms:


Dioxenes. (Diethylene dioxide; glycollide.)


Thioxines. (Diethoxythioxane.)


(Thianthrenes.) Thianthrene and parathianthrene (diethylenedisulphide).

Compounds containing two nitrogen atoms:

The first group only possess heterocyclic atoms in *para*-positions; in the present instance, derivatives of the corresponding *ortho*- and *meta*- series are also known:

Orthodiazines. Pyridazines, cinnolines, and phthalazines.

Metadiazines. Pyrimidines, quinazolines.

Paradiazines. Pyrazines (piperazines), quinoxalines, and phenazines.

Compounds containing one nitrogen and one oxygen (or sulphur) atom:

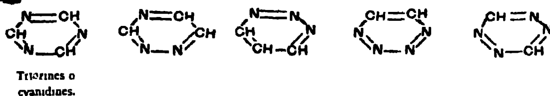
Orthoxazines. Orthothiazines.

Metoxazines. Metathiazines.

Paroxazines. (Morpholines) phenoxazines.

Parathiazines. Phenthiazines (thiodiphenylamines).

Compounds containing more than two nitrogen atoms:



Triazines or cyanidines.

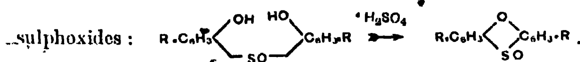
There are also a number of important dyes derived from the *dibenzoparoxazines, thiazines*, and *diazines*, such as *resorufin, methylene blue*, the *indulines*, and the *safranines*, which have been presented together in a separate section.

II. Dioxenes, Thioxenes, and Thianthrenes

The three ring-systems, O(C=C)(C=C)O, O(C=C)(C=C)S, and S(C=C)(C=C)S, are at present but scantily represented. Indeed, the only derivatives of the hypothetical *dioxene* (which would correspond to *oxene*, the unknown parent of the γ-pyrones) are fully saturated substances such as the anhydrides (ethers) of ethylene glycols, O(CHR·CHR)(CHR—CHR)O, and the glycollides or lactides of α-hydroxyacids, O(CO—CHR)(CHR—CO)O.

Again, the only simple thioxene compounds known belong also to the fully saturated series. Such are "*diethylene oxide sulphone*," $O\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle SO_2$, and diethoxythioxane, $O\langle{}^{CH(OEt)-CH_2}_{CH(OEt)-CH_2}\rangle S$, the second of which is formed when the transposition product of chloroacetal (2 mols.) and sodium sulphide (1 mol.) is heated with alcoholic hydrochloric acid; it is a stable white compound which very readily sublimes.

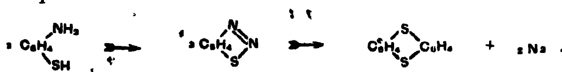
A few derivatives of *dibenzothioxene* or *phenoxthine* have been prepared by the dehydrating action of concentrated sulphuric acid on *o*-oxyaromatic sulphoxides :



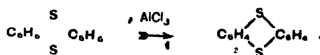
Other dehydrating agents, such as phosphorus oxychloride or thionyl-chloride, usually fail, however, to bring about the elimination of water.

The *dithio*-group is better defined. Here also the fully saturated simple ring is represented by "diethylene disulphide," $S\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle S$, from ethylene mercaptan, ethylene bromide, and alcoholic alkali. In the *dibenzo*-series of this group we find derivatives of the true hetero-cyclic ring, $C_6H_4\langle{}^{S}_{S}\rangle C_6H_4$. These compounds, the thianthrenes (*diphenylene-o-disulphides*), may be prepared :

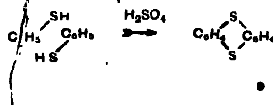
(*a*) By heating the *diazosulphides* formed by the action of nitrous acid on *o*-aminothiophenols :



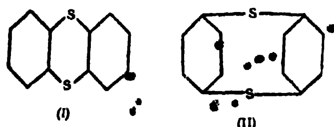
(*b*) By the action of sulphur or sulphur dichloride on benzene in presence of aluminium chloride :



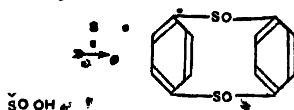
(*c*) By heating aromatic mercaptans or disulphides with aluminium chloride or concentrated sulphuric acid :



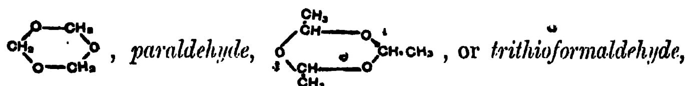
It is generally recognized at the present time that the two last reactions depend on the transitory formation of unstable *sulphoxylic acid* derivatives, R.S.OH, which immediately condense further as shown. Also by these two methods of preparation, the thianthrenes or diphenylene-*o*-disulphides (I) are usually accompanied by large quantities of insoluble isomeric substances, which have been proved to contain a ring-system at present unique in the heterocyclic series, the two sulphur atoms being united to *para*-positions in the benzene nuclei. These bodies are, therefore, *parathianthrenes* or *diphenylene-p-disulphides* (II).



Confirmation of this structure is provided by the fact that aromatic mercaptans or sulphinic acids in which the position *para*- to the sulphur atom is unsubstituted (but not otherwise) readily suffer intramolecular condensation in cold concentrated sulphuric acid to parathianthrenes or parathianthrene dioxides:



It may be mentioned here that the tripolymerides of the simple aldehydes and thioaldehydes, such as *trioxymethylene*,

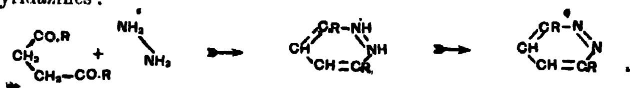


, *paraldehyde*, , or *trithioformaldehyde*,

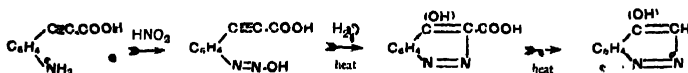
S—CH₂ CH₂ S S—CH₂, possess six-membered heterocyclic systems containing three oxygen or sulphur atoms.

III. Diazines

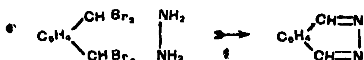
A. **Orthodiazines,** $C\begin{smallmatrix}N=N\\C-C\end{smallmatrix}C$ **(Pyridazines).**—The dihydropyridazines result when hydrazine condenses with γ-diketones, and these oxidize easily to pyridazines:



Two series of *benzorthodiazines* are derivable from pyridazine and members of both are known, namely, the cinnolines, $C_6H_4\begin{smallmatrix}CH=CH\\N=N\end{smallmatrix}$, and the *phthalazines*, $C_6H_4\begin{smallmatrix}CH=N\\CH=N\end{smallmatrix}$. Oxycinnoline is formed from *o*-aminophenylpropiolic acid by diazotization:



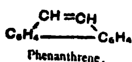
whilst phthalazine may be obtained from ω-tetrabromo-*o*-xylene and hydrazine:

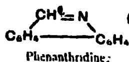


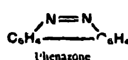
Dibenzorthodiazine or *phenazone* is genetically related to phenanthrene, and is formed when di-*o*-nitrodiphenyl is reduced with sodium and alcohol; it may be regarded as an internal azobenzene, and, in addition to being produced by an analogous reaction to the reduction of nitrobenzene, is a yellow crystalline substance like azobenzene:

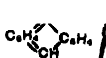


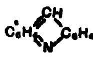
An opportunity may be made here to compare the *meso*-azo substituents in phenanthrene and anthracene respectively:


Phenanthrene.

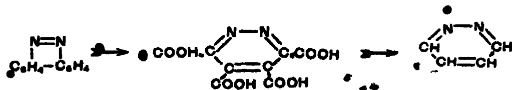

Phenanthridine.


Phenazone



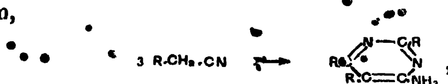


By oxidation with permanganate, phenazone becomes *pyridazine tetracarboxylic acid*, and this readily loses carbon dioxide on warming, and gives *pyridazine* itself, an oil resembling pyridine, and boiling at 208°:

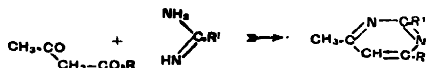


All the ortho- and monobenzorthodiazines are strongly basic compounds of characteristic odour, much resembling both the corresponding pyridines and quinolines or isoquinolines physically and chemically.

B. **Metadiazines,** (**Pyrimidines**).—These are formed in the polymerization of alkyl cyanides when heated with sodium,

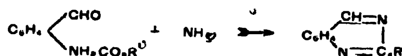


and by condensation of amidines with β-diketones or β-ketonic esters:

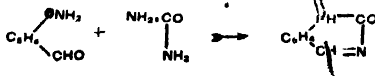


The pyrimidines are, like the *ortho*diazines, strong bases; the monoketoderivatives of reduced pyrimidines are the cyclic ureides, whilst a conjugated pyrimidine-glyoxaline nucleus is the basis of the purines or uric-acid derivatives, which are described at length in the next chapter.

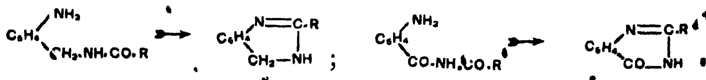
There is only one series of *benzometadiazines*, C_6H_4 (CH=N, N=CH), which are usually known as *quinazolines*, and are produced by the action of ammonia upon *o*-acylaminobenzaldehydes:



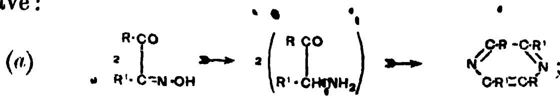
o-Aminobenzoaldehyde and urea react similarly to form *a-ketodihydroquinazoline*,



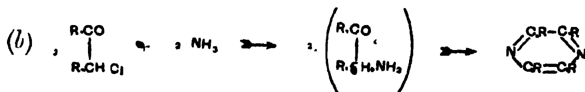
whilst *o*-aminoacylbenzylamines and *o*-amino-acylbenzamides readily condense in presence of acids, giving respectively *dihydroquinazolines* and *β-keto dihydroquinazolines*:



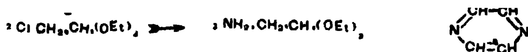
C. **Paradiazines,** C=C N N C—C **(Pyrazines).**—This is the most important group of diazines, by virtue of its relationship to the various series of dye-stuffs enumerated in the following section. The general methods for the preparation of the simple *para*-diazines involve the condensation of *α*-aminoketones, either intermolecularly (*a*) or by ammonia (*b*). Thus, if the mono-isonitrosodiketones are reduced and then oxidized gently, we have:

(*a*) 

and when *α*-bromoketones are boiled with alcoholic ammonia,

(*b*) 

The parent substance *pyrazine* (*aldine*) is similarly produced when *α*-aminoacetal (from chloracetal and ammonia) is oxidized or further treated with ammonia:

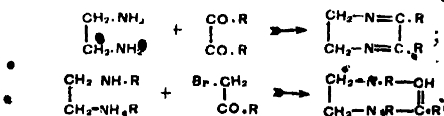


It is a solid which sublimes very readily and smells like heliotrope (piperonal).

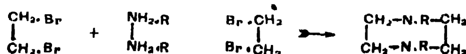
The pyrazines are not so strongly basic as the *ortho*- or *meta*-diazines, and upon reduction yield dihydro-, tetrahydro-, and finally hexahydropyrazines.

These substances are some of the heterocyclic compounds which are most easily obtainable from the simple aliphatic

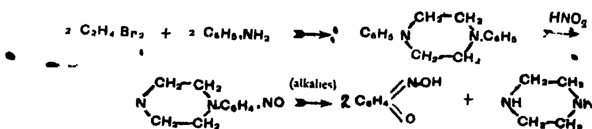
series; thus substituted ethylene diamines readily yield either of the first two series by condensation with α-diketones or ω-bromoacetophenones:



On the other hand, the hexahydroderivatives, usually known as *piperazines,* result when ethylene bromide is digested with amines:



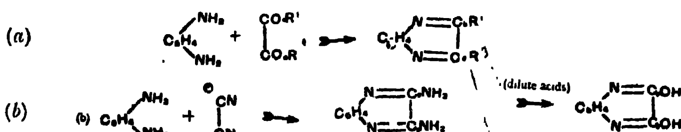
Piperazine itself may be thus obtained from ammonia and ethylene bromide or from di-*p*-nitrosophenylpiperazine on boiling with alkalies:



It is a strongly alkaline liquid, very similar to piperidine, and reverts to pyrazine when distilled over zinc dust.

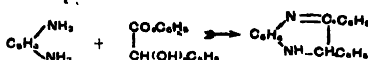
It will be remembered that *ethylene imide,* $NH\Big<\begin{matrix}CH_2\\|\\CH_2\end{matrix}$, is never formed in the above reaction (p. 21), doubtless owing to the inferior stability of the triatomic ring.

D. **Benzoparadiazines,** $C_6H_4\Big<\begin{matrix}N=CH\\|\\N=CH\end{matrix}$ **(Quinoxalines).** — Quinoxalines are synthesized by the condensation of *o*-phenylenediamines with (*a*) α-dicarbonyl compounds (ketones, ketonic acids, or oxalic acid), and (*b*) cyanogen:

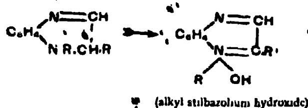


They are weak bases, readily reducible to hydrobenzopara-diazines.

The *dihydroquinoxalines* may also be prepared from *o*-phenylenediamines by condensation with α-ketoalcohols, such as benzoin:

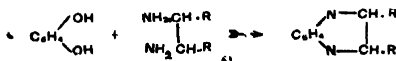


Dihydroquinoxalines are usually crystalline, and, if the imino hydrogen is unsubstituted, are easily oxidized to quinoxalines; when, however, this is replaced by an alkyl group, oxidation leads to the production of unsaturated alkylammonium bases:

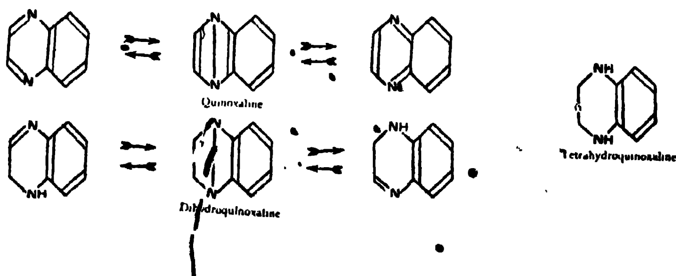


(alkyl stilbazolium hydroxide)

Finally, the tetrahydrocompounds are also known, and are usually prepared from catechol and ethylenediamines:

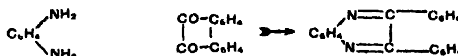


From the point of view of Hewitt's theory of fluorescence, it is very suggestive that whilst quinoxalines and tetrahydroquinoxalines are not fluorescent, the dihydroquinoxalines (the only series of the three which, having due regard to the disposition of the valencies in the benzonucleus, can display "double symmetric tautomerism") are all fluorescent:

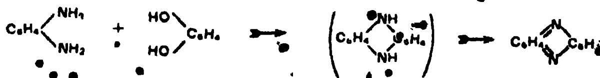


E. **Dibenzoparadiazines,** $C_6H_4 \langle N_2 \rangle C_6H_4$ **(Phenazines).**—The preparation of these compounds from *o*-phenylenediamines may be carried out along several lines.

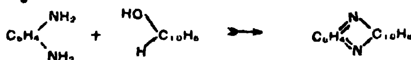
For instance, the latter compounds readily condense with *o*-quinones as follows :—



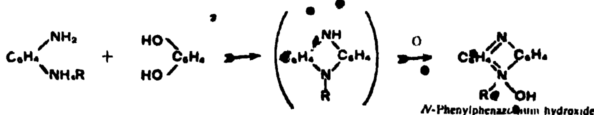
On the other hand, *o*-dioxybenzenes, which are the quinols corresponding to *o*-quinones (these being frequently, however, unknown), give phenazines when heated with diamines, oxidation simultaneously taking place :



Finally, with more complicated phenols such as the naphthols, it is only necessary to employ the monohydric phenol :



If, in any of these condensations, mono-alkyl-*o*-phenylene diamines are used, the product is found to be not a phenazine, but a substituted ammonium base similar to the *stilbazonium* derivatives produced by analogous methods in the monobenzoparadiazine series :



The phenazines are bright yellow crystalline bodies of high melting-point, and fluoresce in solution.

Phenazine itself melts at 171°, and, in addition to the above general methods, may be synthesized :

(*a*) By passing aniline through red-hot tubes.

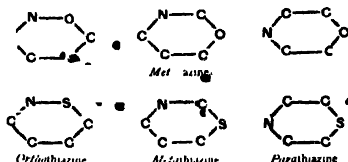
(*b*) By boiling a solution of *o*-phenylaminoazobenzene with mineral acids :



It is easily reducible to *dihydrophenazine*, $C_6H_4\langle{NH \atop NH}\rangle C_6H_4$, but this, in common with other dihydrophenazines and the corresponding dihydroacridines, passes back exceedingly readily to the oxidized condition.

IV. Oxazines and Thiazines

As in the case of the diazines, there are three possible series of *oxazines* and *thiazines* to be considered :

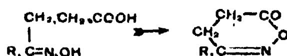


Similarly to the diazines, also, it is the *para*- compounds (and especially the *dibenzopara*-derivatives) which are the most important.

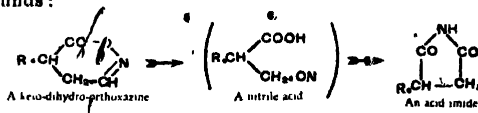
A. *Ortho*- and *meta*-oxazines and -thiazines.

There are but few derivatives known of these four systems, and in most cases the members which have been prepared are referred to the reduction products of the hypothetical ring parents and do not correspond to the fully unsaturated ring systems.

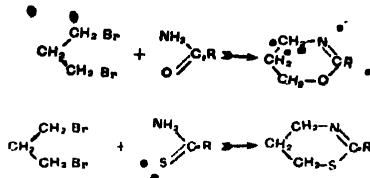
No derivatives of *ortho*thiazine, reduced or otherwise, have yet been met with, whilst the only representatives of the corresponding oxazines are anhydride-like derivatives obtained from the oximes of γ-ketonic acids :



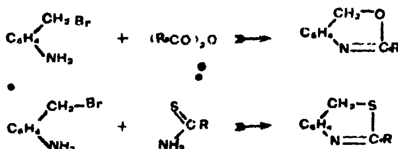
These are very similar to the ketodihydro*isooxazoles* (p. 65), and, if suitable substituents are present, they are readily decomposed in analogous fashion to these compounds :



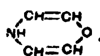
Partially reduced *metoxazines* and *metathiazines* (known as *pentoxazolines* and *penthiazolines*, just as derivatives of the six-membered ring homologue of thiophene (p. 96) are called *penthiophenes*) have been prepared by the action of trimethylene bromide on acid amides or thiamides:



The corresponding *benzometa-oxazines* and *-thiazines* are produced respectively from acid anhydrides and thiamides in presence of ω-bromo-*o*-toluidine:

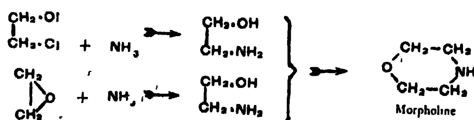


β. **Paroxazines,** $N\left<\substack{C-C\\C-C}\right>O$.—Here, again, there are no compounds known corresponding to the true azine structure,

. The tetrahydro derivatives are, however, of some importance, and correspond to the piperazines (p. 173). There is reason to believe that this reduced ring system occurs in the molecules of the morphine group of alkaloids, and its compounds have accordingly received the name of *morpholines*.

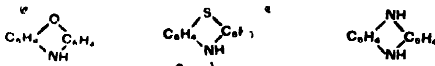
The parent member, *morpholine*, $O\left<\substack{CH_2-CH_2\\CH_2-CH_2}\right>NH$, is formed by heating *oxyethylamine* with mineral acids or bases. The latter

substance is prepared from ammonia and ethylene oxide or chlorhydrin:

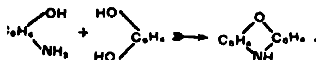


The morpholines and benzomorpholines are generally viscous liquids which can be distilled undecomposed.

The *phenoxazines* or *dibenzoparoxazines* are noticeable in virtue of their relationship to some valuable dyes, and it may be pointed out at this juncture that phenoxazine (or phenthiazine) and phenazine are not strictly parallel compounds. The discrepancy is due to the fact that whilst oxygen is an element of even valency (two or four), nitrogen is an odd-valent element. Thus the "true" phenoxazine would be $C_6H_4\langle {O \atop N} \rangle C_6H_4$, or conversely, the actual phenoxazine corresponds more nearly to *dihydrophenazine*:



Phenoxazines are formed if, in the preparation of phenazines by heating together *o*-dioxybenzenes and *o*-phenylenediamines, *o*-aminophenols are substituted for the latter compounds:



C. **Parathiazines,** $S\langle {C-C \atop C-C} \rangle N$.—There are no important simple or monobenzo-compounds of this group, but as usual the *dibenzo*-series are of interest. The parent substance, *dibenzoparathiazine* or phenthiazine, is usually known under the name of *thiodiphenylamine*, and may be formed according to the general method by

heating catechol with *o*-aminothiophenol, but is usually made by heating diphenylamine with sulphur at a fairly high temperature (200-300°). The corresponding thioditolylamines, thiodinaphthylamines, etc., have also been prepared. All are colourless, high-melting, solid substances.

V. The Azine Dyes

It has been hinted that phenazine, phenoxazine, and phenthiazine are closely related to numerous important dyes, and we shall review these in the present section. All of these colouring matters are oxy- or amino-derivatives of the dibenzo-azines; in other words, the trinuclear ring-systems dealt with are of a strongly *chromogenic* nature, and the introduction of the *auxochromes*, or salt-forming HO- and NH_2- groups, causes the production of intense colour. At the same time it must be noted that in each case removal of two hydrogen atoms (one from the "auxochrome" and one from the ring-imino group) occurs before colour appears, the simple oxy- or amino-phenazines being colourless (*leuco-bases*). Consequently the development of colour in this series is always coincident with the possibility of a (*para*-) quinonoid structure appearing in the molecule.

The nature of the dyes in question may be grasped most easily by dividing them into two main classes:

A. *Derivatives of simple phenazines*, $C_6H_4\langle {N \atop N} \rangle C_6H_4$

B. *Derivatives of phenazonium*, $C_6H_4\langle {N \atop N} \rangle C_6H_4$ (with R and Cl on the lower N)

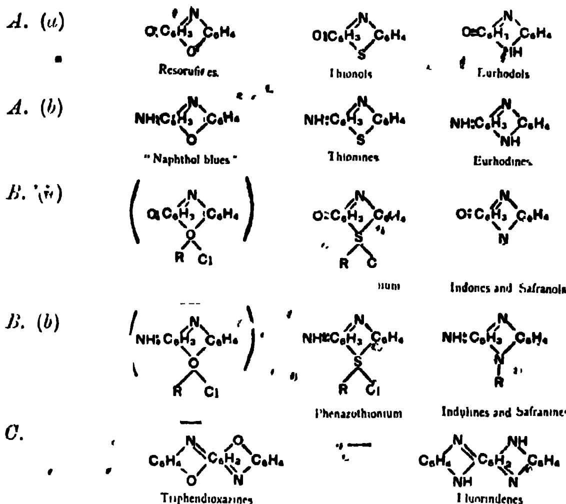
C. *Conjugated phenazine nuclei.*

Colouring matters are formed from the first two of these classes in all three series—phenazine, phenoxazine or phenthiazine—by the introduction of the following groups:

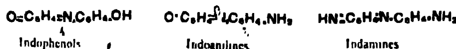
(a) *Hydroxyl*, -OH.

(b) *Amino or alkylamino*, $-NH_2$, -NHR, or $-NR_2$.

The third class are coloured even in the absence of these groups. We thus have the following general possibilities:—

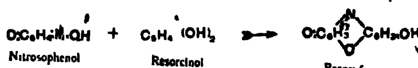


Most of these compounds are genetically related to certain other dyes of the nonheterocyclic series, from which they may sometimes actually be formed by chemical introduction of the second heterocyclic ring-member. These homocyclic colouring matters are the *p*-oxy- and *p*-imino- derivatives of diphenylamine.



We will now review the individual classes, the most important members in which are indicated above under their typical formulæ.

A. (*a*) **Oxyphenazines.**—The dyes of the *phenoxazine* series are produced from *o*-aminophenols by heating with oxy-*o*-quinones (or oxy-*o*-dihydric phenols; compare p. 178), but more usually by the action of nitrosophenols (quinone monoximes), or of nitrous acid, upon polyhydric phenols:



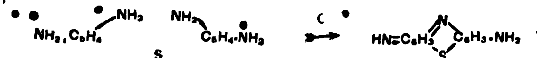
The corresponding sulphur dyes (the *thionols*) are formed from the *thionines* (see below) when these are heated with alkalies, whilst the *eurhodols* are similarly obtained from the aminophenazines (*eurhodines*) or from *o*-phenylenediamines and oxy-*o*-quinones.

The following table includes the most important members of this group:

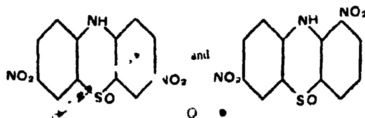
Resorufin	$O:C_6H_3.[NO]^*.C_6H_3(OH)$.	Rose-red.
Gallocyanine	$O:C_6H(OH)(COOH).[NO].C_6H_3(NMe_2)$	Violet.
Eurhodol	$O:C_6H_3.[N_2H].C_6H_4$.	Scarlet.

A. (*b*) **Aminophenazines.**—When *p*-nitrosoanilines and α- or β-naphthol are condensed, dyes of the aminophenoxazine group (*naphthol blue*, *Nile blue*, etc.) are produced.

Again, when *p*-phenylenediamines are warmed with aqueous hydrogen sulphide and ferric chloride, the important *thionine* or *methylene blue* compounds result:

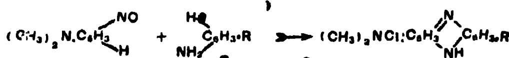


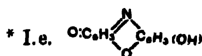
These are also made by treating thiodiphenylamine with strong nitric acid, when a mixture of isomeric dinitrodiphenylamine sulphoxides is formed:



These are easily separated, and whilst the former yields *thionine* by reduction and subsequent atmospheric oxidation, the latter yields a less important dye, *isothionine*, by the same procedure. Methylation of *thionine* produces *methylene blue*, which is also made according to the first method from *p*-dimethylaminoaniline, and on the large scale from *p*-nitrosodimethylaniline and sodium thiosulphate.

Finally, the eurhodines result when amino-*o*-diamines are heated with *o*-quinones, or if *p*-nitrosodimethylaniline condenses with *para*-substituted anilines:

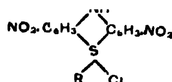


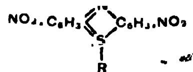
* I.e. 

The following have proved of commercial importance at one time or another :—

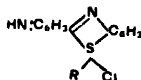
Naphthol blue	$Me_2NCl:C_6H_3.[NO].C_{10}H_6$	Violet blue.
Nile blue	$Me_2NCl:C_6H_3.[NO].C_{10}H_5.NH_2$	Blue.
Cyanamine	$Me_2NCl:C_6H_3.[NO].C_{10}H_5.NH.C_6H_5$	Blue.
Thionine (Lauth's violet)	$HN:C_6H_3.[NS].C_6H_3.NH_2$	Violet blue.
Methylene blue	$Me_2NCl:C_6H_3[NS].C_6H_3NMe$	Deep blue.
Eurhodine	$HN:C_6H_3.[N_2H].C_6H_4$	Scarlet.
Toluylene red	$Me_2NCl:C_6H_3.[N_2H].C_6H_3.NH_2$	Scarlet red.

B. (*a*) and (*b*). *Phenazonium Dyes.*—No derivatives of phenazooxonium have yet been prepared, but a series of *S*-phenylphenazothionium compounds, although of no commercial value, is interesting from analogy with the indulines and safranines. When the above-mentioned dinitrodiphenylamine sulphoxides are condensed with phenols in strong sulphuric acid solution, green coloured salts of the following structure (I) are formed, which give purple-red anhydrobases with alkali (II) :



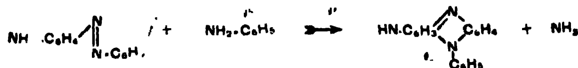


On reduction, these give deep blue dyes of the formula



The *indulines* and *safranines* are exceedingly important colouring matters, some of which have been known for a very long while. Both are derived from *amino-N-phenylphenazonium*, *indulines* being *mono-*, and *safranines* the symmetrical *di*-amino compounds. It is necessary to remark here that *N*-alphylphenazonium compounds are not, generally speaking, dyes; the presence of an aromatic substituent seems necessary for the production of intense colour.

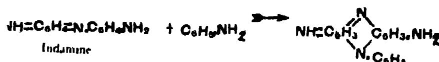
Indulines are made by heating *p*-aminoazobenzenes and anilines with acids :



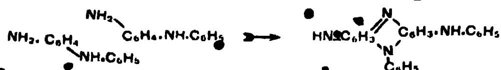
and by condensing phenyl-*o*-diamines with amino-*o*-quinones.

Safranines are formed when *p*-phenylenediamines and anilines are oxidized together by chromic acid or bleaching powder; in practice the exact preliminary amounts of each constituent are ensured by preparing the mixture by the reduction of the appropriate aminoazo-compound:





They are also made on a similar principle from *m*-aminodiphenylamines and *p*-phenylenediamines when a mixture of these is oxidized:



As will be seen from the appended summary, some of these derivatives were the earliest known "aniline dyes"; it is impossible here to enter into the details of the researches involved in establishing their constitution, and it can only be said that, as soon as the structure of the triphenylmethane dyes (also produced in the oxidation of anilines) was settled, the present problem was attacked by E. and O. Fischer, Nietzki, Caro, Bernthsen, and many others. Whilst the main outlines of the question are now known with certainty, the details of the constitution of the different salts obtainable from each compound (for, according to the amount of acid present, several well-defined series of red, green, or blue salts are produced) are still being debated by Kehrmann and others.

Indulines.

Aposafranine, $HN:C_6H_3:(N_2C_6H_5).^*C_6H_4$	Red.
Naphthyl violet, $HN:C_{10}H_4(N_2C_6H_5).C_{10}H_5.NH.C_6H_5$	Deep violet.

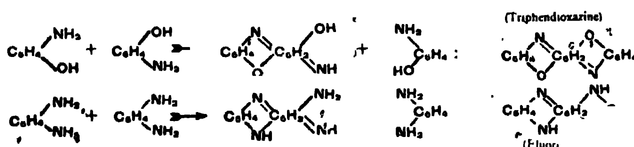


Safranines.

Fuchsia, $Me_2NCl:C_6H_3:(N_2C_6H_5).C_6H_3.NMe_2$	Reddish purple.
Amethyst, $Et_2NCl:C_6H_3:(N_2C_6H_5).C_6H_3NEt_2$	Purple.
Safranine, $HN:C_6H_2Me:(N_2C_6H_5).C_6H_2Me.NH_2$	Orange-red.
Mauvine, $HN:C_6H_3:(N_2C_6H_5).C_6H_3.NH.C_6H$	Purple (Perkin, 1856).
Indazine, $Me_2NCl:C_6H_3:(N_2C_6H_5).C_6H_3.NH.C_6H_5$	Purple.
Magdala red, $HN:C_{10}H_5:(N_2C_{10}H_7).C_{10}H_5.NH_2$	Crimson.

Indones and *safranols* are made, like the thionols (p. 181), by heating the corresponding induline or safranine with mineral acids. They are not now of great commercial value.

C. Conjugated Phenazines.—These are produced by heating the hydrochloric acid salts of *o*-aminophenols and *o*-phenylenediamines respectively; their formation is due to intermolecular oxidation and condensation:



These are deep green, stable compounds, with a brilliant red fluorescence, but are not much used in dyeing. It should be remembered that the tinctorial value of all indulines and safranines is much increased by their beautiful fluorescence, which varies, according to the compound, from green to violet.

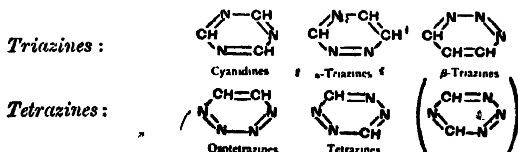
VI. Triazines and Tetrazines

We have, in conclusion, to consider the derivatives of pyridine in which two or three of the ring *methine* groups are replaced by nitrogen atoms, and which are known as triazines and tetrazines according to the total number of nitrogen atoms present.

Obviously there are three possible ring-systems in each class:

Triazines:

Tetrazines:

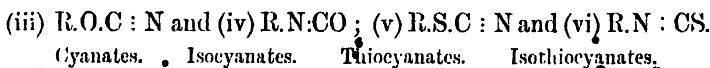


The only series of any importance is the first of these, the *cyanidines* or *symmetrical-triazines*, which are very closely related to hydrocyanic acid and its polymers. We shall deal at some length with these compounds, and then briefly review the remaining groups.

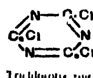
Symmetrical Triazines.—It is well known that derivatives of prussic acid exist corresponding to both structures :



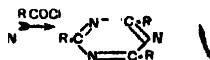
that whilst the alkyl compounds of (i) are non-poisonous, the free acid and the alkyl esters of (ii) are exceedingly toxic. Moreover, if we consider the more oxidized cyanic and thiocyanic acids, we again encounter two sets of compounds in each series :



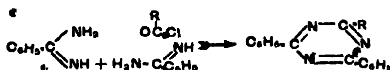
By the action of halogens on prussic acid or its salts in the cold, the cyanogen halides, CNCl, CNBr, and CNI are formed ; these are poisonous, irritating compounds, which all melt and boil below 60°. If they are heated under pressure, or if the halogens react with prussic acid at higher temperatures, polymers of these compounds result, in which three molecules of cyanogen halide are condensed together. It will appear shortly that the polymerides, which are insoluble solids of high melting point, are really *trihalotriazines* : for example :



Now, when a mixture of an acid nitrile and an acid chloride is treated with aluminium chloride, alkylic derivatives of the triazines are formed :

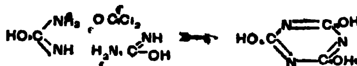


They are also formed when amidines of the aromatic series are heated with acid halides or anhydrides; for example:



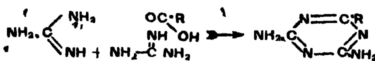
Triphenyltriazine (*triphenylcyanidine* or *cyanphenine*) was thus prepared more than fifty years ago.

In this reaction carbonyl chloride may be used instead of an organic acid chloride, and then an *oxytriazine* is formed; whilst, if urea and carbonyl chloride are similarly heated together, a *trioxytriazine* must be produced:



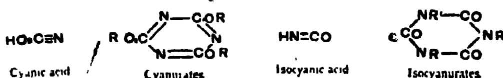
As a matter of fact, the compound formed proves to be identical with *cyanuric acid*, obtained in the distillation of uric acid (Scheele, 1780), by polymerization of cyanic acid, or by heating the tricyanogen halides with alkalies. Cyanuric acid may also be converted to tricyanogen chloride by treatment with phosphorus pentachloride. This establishes the structure of the tricyanic or cyanuric acid derivatives as oxytriazines.

Diaminotriazines are similarly produced by distillation of guanidine salts with organic acids:

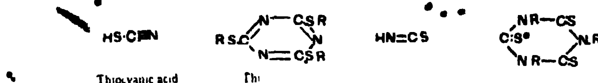


Alkyloxytriazines of two kinds are known: the first are esters of cyanuric acid, formed from its halides and sodium alkyloxides.

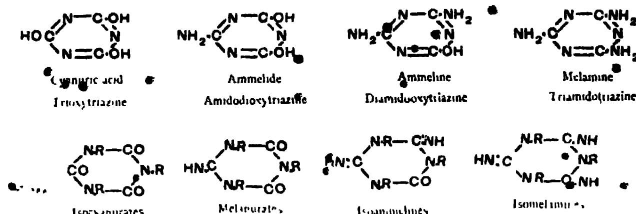
If, however, an alkyl halide is heated with silver cyanurate, a mixture of these esters with higher melting isomeric products is produced, the latter being derived from hypothetical *isocyanuric acid*, which is related to cyanuric, as iso-cyanic is to cyanic acid:



Corresponding to these we have *thiocyanuric acid*, formed from tricyanogen chloride and potassium hydrosulphide, KSH, and its esters, similarly formed from potassium mercaptides, K.S.R., and by polymerization of alkyl thiocyanates; whilst a second series of isomeric esters (from the unknown *isothiocyanuric acid*) result when the alkyl isothiocyanates (mustard oils) polymerize:



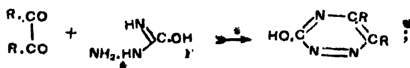
Finally, the amides of cyanuric acid must be mentioned; the mono-, di-, and tri-amides (and esters of the corresponding imides of isocyanuric acid) are all known:



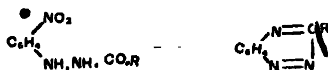
Melamine is made from cyanuric chloride and ammonia, or by polymerization of cyanamide, $CN.NH_2$; by boiling with water it forms a mixture of *ammeline, ammelide*, and *cyanuric acid*. Alkyl melamines, ammelines, and ammelides are produced by the action of amines on the tricyanogen halides, and the isomeric *alkyl isomelamines* are formed when alkylcyanamides, CN.NHR, polymerize.

Melamine and more complicated products (formed by elimination of ammonia from two or more molecules of melamine, and known as *melam, melem*, and *mellon*) are produced when ammonium thiocyanate, $NH_4.S.C:N$, is destructively distilled.

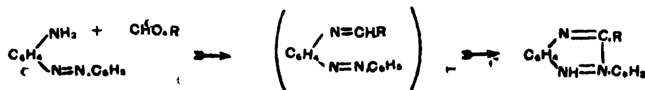
a- and β-Triazines. Simple a-triazines have been synthesized from semicarbazide by condensation with a-diketones:



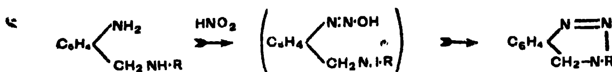
and *monobenzo*-derivatives of this system result from the reduction of *o*-nitrophenylacylhydrazines:



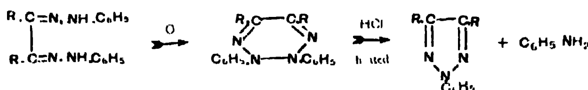
These are stable, crystalline, yellow compounds, as also are their colourless *dihydroderivatives*, produced from *o*-aminoazocompounds and aldehydes:



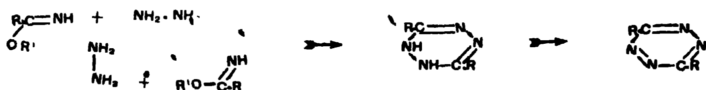
Analogous *dihydrobenzo-β-triazines* are formed from *o*-aminobenzylamines and nitrous acid. These are less stable than the *a*-triazines.



Tetrazines.—No derivatives of the system (CH=N, N, CH, N—N) have apparently been obtained; the osotetrazines (CH—CH, N, N, N=N) are represented by their dihydrocompounds (*osotetrazones*), which are made from *a*-diketonediphenylhydrazones, and readily pass into triazoles (p. 78).

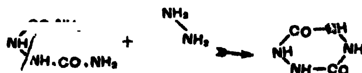


The symmetrical *tetrazines*, (CH—N, N, N, N=CH), are more numerous, and are formed by the gentle (atmospheric) oxidation of the corresponding dihydrocompounds, obtained by condensation of hydrazine with imino ethers:



From the deep red colour and fluorescent nature of these tetrazines, it may well be that their formula is really (R.C=N, N———N, N=C.R).

Diketotetrahydrotetrazines (*urazines*) are urea derivatives, formed from hydrazine carbamate and hydrazine:



CHAPTER X.

THE PURINES AND OTHER CYCLIC DERIVATIVES OF UREA

I. THE PROTEINS

THE tissues of animal bodies are composed to a large extent of a numerous class of very complicated organic compounds, termed *proteins*. The molecular magnitude and the general chemical structure of these substances is at present but imperfectly known, but the products into which they break down by means of fermentation or chemical hydrolysis have been very carefully studied during the past thirty years by various workers, and most notably by Emil Fischer. It is found that the proteins may be classified in four main divisions according to the decomposition products which they thus furnish:

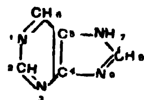
	Main Products of Decomposition.
Nucleo-proteids	Proteids, phosphoric acid, and purines.
Nucleo-albumens	,, phosphoric acid, and polypeptides.
Glyco-proteins	,, phosphoric acid, and sugars.
Lecith-albumens	,, and lecithins (mixed glycerides of phosphoric, stearic, and palmitic acids).

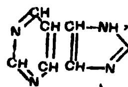
The nature of the *proteids* which are also formed in each case is still uncertain; they are very complex nitrogenous bodies, to which the polypeptides are probably nearly related.

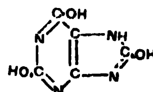
Our purpose, however, is to discuss the simpler products formed, and in succeeding chapters we shall deal with the *polypeptides* and the *sugars*, whilst we now proceed to give some account of the *purine* or *uric acid* group.

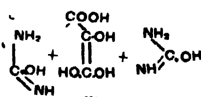
Fischer has shown that these compounds (many of which are

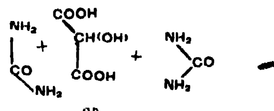
frequently met with in products of the animal metabolism, whilst some are also found, but less often, in certain plants) may all be considered as derived from a substance, *purine* (I), which is to be looked upon as a "condensed" heterocyclic system made up of a pyrimidine (metadiazine) and a glyoxaline ring (II), just as, for example, quinoline is a "condensed" ring-system from benzene and pyridine. If now we imagine a trioxypurine system (III) to be broken up by the addition of four molecules of water, it is easy to see that the resulting products (IV) are tautomeric forms of urea and oxycarboxylic acids (V).











A glimpse into the mode of union of the purines with other protein constituents is afforded by this knowledge of their general structure. It is known that glyoxalines and purines which possess the free imino-group condense with aromatic diazocompounds and form coloured diazoimino derivatives containing the grouping $-NH-N=N.C_6H_5$, but on the contrary purines when combined with phosphoric acid in a protein do not do so. Consequently it is assumed that they form phosphoryl compounds of the type $=N-PO(OR)_2$. Moreover, the nucleoproteins break down much more readily in presence of mineral acids than of alkalies, and a similar behaviour is shown by synthetic phosphoryl derivatives of amines, R.NH.PO(OH).R.

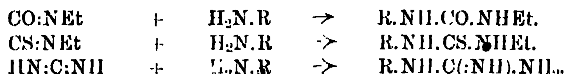
Returning to the discussion of the purines themselves, we see that, in addition to what may be called the heterocyclic conception of their structure, they may also be regarded as condensation products of two molecules of urea with an oxy-acid.

As a matter of fact, the bulk of the experimental work on purines has been conducted from this standpoint, and therefore, before describing the naturally-occurring members of the group, we will refer to the analogous compounds derived from urea and its congeners by the action of different types of organic acids.

II. Simple Condensations of the Amides and Imides of Carbamic Acid

It is assumed that the reader is already well acquainted with the nature of the amide, $CO(NH_2)_2$ (*urea*), the thioamide, $CS(NH_2)_2$ (*thiourea*), and the imide, $HN:C(NH_2)_2$ (*guanidine*), of the unknown carbamic acid, $NH_2.COOH$, and the reactions now to be described are only those bearing on the subject of this chapter. It will accordingly suffice to deal with the *alkyl-*, and *alkylene* , and *acyl-ureas*, *thioureas*, and *guanidines*.

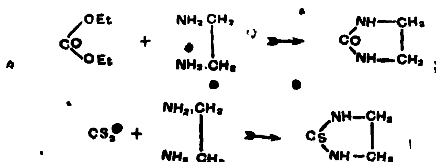
Alkyl Derivatives.—These are produced by heating isocyanic or isothiocyanic esters, or cyanamide, with amines:



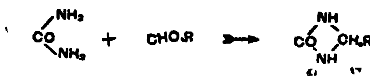
$CO:NEt$	+	$H_2N.R$	→	$R.NH.CO.NHEt.$
$CS:NEt$	+	$H_2N.R$	→	$R.NH.CS.NHEt.$
$HN:C:NH$	+	$H_2N.R$	→	$R.NH.C(:NH).NH_2.$

The urea compounds are also formed when chlorourea (*urea chloride*, $Cl.CO.NH_2$, made from ammonia and excess of carbonyl chloride) acts upon amines. Simple alkyl ureas are very similar to urea itself; they are well crystallized, and yield monobasic salts with strong acids.

Alkylene Derivatives.—These are more interesting than the former class (which they closely resemble in ordinary properties) by reason of their cyclic character; alkylene guanidines, however, have not been synthesized. The members of the other two series result when alkylenediamines are heated with carbonic or thiocarbonic esters, or carbon disulphide:



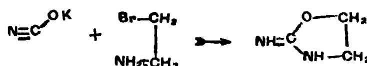
Moreover, urea unites with aldehydes in the cold to similar, but tetratomic, ring-systems.



It will be noticed that the five-membered rings are ketotetrahydro-*glyoxalines*.

It must not be forgotten that all three amide derivatives of carbamic acid can react in two forms, for example, $NH_2.CO.NH_2$ (urea) and $HN:C(OH).NH_2$ (ψ-urea), and appear frequently to display the latter constitution in the more complicated transformations of the purine group.

Isomeric alkylene ureas and thioureas of the ψ-series are well known, and are formed when ω bromoalkylamines act on cyanates or thiocyanates :



Acyl Derivatives.—In the case of urea, these are known as ureides, and some of these are very closely related to uric acid and the other purines. They have been prepared by simply heating urea or thiourea with acid chlorides :



$$NH_2.CO.NH_2 + R.CO.Cl \rightarrow NH_2.CO.NH.CO.R.$$

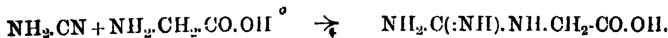
The same acylthiourea is formed either by this method or by heating cyanamide and thioaliphatic acids :



$$R.CO.SH + NC.NH_2 \rightarrow R.CO.S.(HN:)C.NH_2,$$

and it is therefore believed that the acylthioureas, at all events, exist in the *pseudo*-form.

Amino-aliphatic acids and cyanamide give analogous products, the *guaneides*, for example, *glycocyamine* (guanidoacetic acid) :



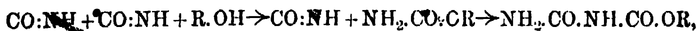
$$NH_2.CN + NH_2.CH_2.CO.OH \rightarrow NH_2.C(:NH).NH.CH_2\text{-}CO.OH.$$

Certain of these compounds merit individual mention.

Ureides from Carbonic Acid.—These are interesting, since urea itself is the diamide of carbonic acid, and because they are formed from urea by pyrocondensation, and so help to illustrate the

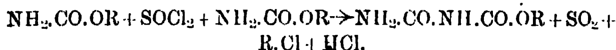
manner in which the more complex condensations of that substance and its allies may take place.

When cyanic acid is warmed with alcohols, esters of the unstable *allophanic acid*, $NH_2.CO.NH.CO.OH$, are produced,



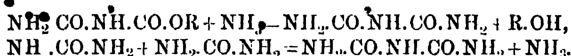
$$CO:NH + CO:NH + R.OH \rightarrow CO:NH + NH_2.CO.OR \rightarrow NH_2.CO.NH.CO.OR,$$

and these are also the product of the action of thionyl chloride on carbamic esters (*urethanes*),



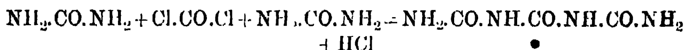
$$NH_2.CO.OR + SOCl_2 + NH_2.CO.OR \rightarrow NH_2.CO.NH.CO.OR + SO_2 + R.Cl + HCl.$$

The esters are stable, high-melting solids, which, by the action of ammonia, yield the amide of allophanic acid or *biuret* (also made by heating urea, and recognized by its purple copper salt):



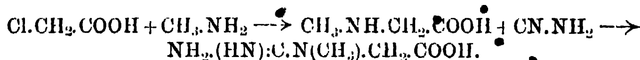
$$NH_2.CO.NH.CO.OR + NH_3 = NH_2.CO.NH.CO.NH_2 + R.OH,$$
$$NH_2.CO.NH_2 + NH_2.CO.NH_2 = NH_2.CO.NH.CO.NH_2 + NH_3.$$

Finally, by heating urea and carbonyl chloride under pressure at 100°, *carbonyl diurea*, which is probably also produced to some extent when urea is heated alone, results:



$$NH_2.CO.NH_2 + Cl.CO.Cl + NH_2.CO.NH_2 = NH_2.CO.NH.CO.NH.CO.NH_2 + HCl$$

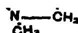
Some of the *guaneides* are also of especial interest, owing to their occurrence in animal juices, notably *creatine*, $NH_2.(HN):C.N.(CH_3).CH_2.COOH$, from meat extracts, which has been synthesized from cyanamide and methyl glycocoll (compare *glycocyamine* above):



$$Cl.CH_2.COOH + CH_3.NH_2 \longrightarrow CH_3.NH.CH_2.COOH + CN.NH_2 \longrightarrow NH_2.(HN):C.N(CH_3).CH_2.COOH.$$

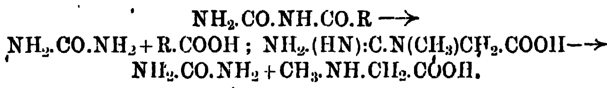
It is a neutral substance which passes into a betaine-like derivative on heating to 100°:





This compound, *creatinine*, is strongly basic; with weak alkalies the imino-group is replaced by oxygen, yielding *methylhydantoin* (see below). It is found in mammalian excreta.

Ureides and guaneides are resolved into their constituents by boiling with aqueous potash or soda; thus:



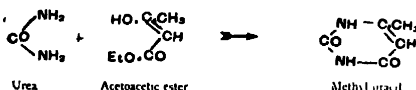
$$NH_2.CO.NH.CO.R \longrightarrow$$
$$NH_2.CO.NH_2 + R.COOH;\ NH_2.(HN){:}C.N(CH_3)CH_2.COOH \longrightarrow$$
$$NH_2.CO.NH_2 + CH_3.NH.CH_2.COOH.$$

III. Cyclic Ureides of Oxyacids and of Dibasic Acids

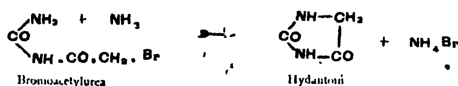
The cyclic condensation products of urea and guanidine with dibasic acids are of much importance from the standpoint of purine chemistry, because certain of them, especially parabanic acid, alloxan, and hydantoin, are so frequently produced when uric acid or other purines are oxidized.

General methods for their synthesis are:

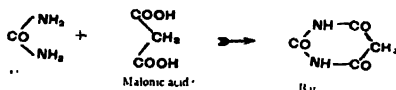
(*a*) The interaction of urea and suitable ketonic esters.



(*b*) The action of ammonia on bromacyl ureas.



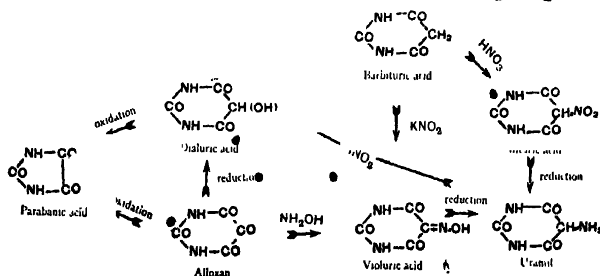
(*c*) The action of phosphorus oxychloride upon a mixture of urea or guanidine and dibasic acids.



The cyclic ureides are fairly stable crystalline compounds, with markedly acidic functions, as would be anticipated from the presence of several contiguous carbonyl-imino systems. The following table includes the chief ureides which have proved useful in elucidating the structure of the purines.

			Generators.	*Formation from Purines.*
Hydantoin	Glycollylurea	$CO\left\langle\begin{matrix}NH-CH_2\\NH-CO\end{matrix}\right.$	Urea and glycollic acid	Reduction of allantoin
Allantoin	Glyoxyldiurea	$CO\left\langle\begin{matrix}NH-CH.NH.CO.NH_2\\NH-CO\end{matrix}\right.$	Urea and glyoxylic acid	Oxidation of uric acid
Uracil	Oxymethylene-acetylurea	$CO\left\langle\begin{matrix}NH-CH\\NH-CO\end{matrix}\right\rangle CH$	(Hypothetical)	
Methyl uracil	Acetoacetylurea	$CO\left\langle\begin{matrix}NH-C.CH_3\\NH-CO\end{matrix}\right\rangle CH$	Urea and acetoacetic ester	
Parabanic acid	Oxalylurea	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right.$	Urea and oxalic acid	Oxidation of alloxan
Malonylguanidine	—	$HN:C\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CH_2$	Guanidine and malonic acid	—
Barbituric acid	Malonylurea	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CH_2$	Urea and malonic acid	From alloxantin
Dialuric acid	Tartronylurea	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CH(OH)$	Urea and tartronic acid	Reduction of alloxan
Alloxan	Mesoxalylurea	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CO$	Urea and mesoxalic acid	Oxidation of uric acid
Violuric acid	Alloxan monoxime	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle C=N.OH$	(See below)	
Dilituric acid	Nitrobarbituric acid	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CH.NO_2$	(See below)	
Uramil	Aminobarbituric acid	$CO\left\langle\begin{matrix}NH-CO\\NH-CO\end{matrix}\right\rangle CH.NH_2$	(See below)	

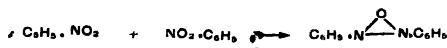
The transformations of the last half-dozen compounds are especially important with reference to purine syntheses, and their mutual relations are indicated in the following diagram:—



Boiling alkalies break the cyclic ureides up into urea and the respective acids, but if baryta is used, only a partial hydrolysis occurs, and a monocarboxylic acid is formed which is at the same time basic owing to the presence of the resulting amino hydrogen in the group, $NH_2.CO.NH$-. Thus we have *oxaluric acid*, $NH_2.CO.NH.CO.COOH$, from parabanic acid; *alloxanic acid*, $NH_2.CO.NH.CO.CO.COOH$, from alloxan; and *glycoluric acid*, $NH_2.CO.NH.CH_2.COOH$, from hydantoin.

When *alloxan* is reduced by mild reagents, a substance, *alloxantin*, results, which may also be obtained by gentle oxidation of uric acid, and which probably holds a somewhat similar relation to alloxan as that of azoxybenzene to nitrobenzene.





Oxalantin is similarly produced from parabanic acid.

IV. Uric Acid

Uric acid is an insoluble white granular powder, normally present in the excreta of animals, birds, and snakes, and also in the juices of flesh-eating mammalia. Owing to its sparingly soluble nature, any temporary excess of uric acid in the organism tends to be deposited, either in the joints or in the form of small nodules ("gravel," "stone," etc.). Its separation is attended by considerable pain (gout, rheumatism, etc.); to allay this, it is frequently sought to remove the acid by an appropriate basic medicine; the sodium or ammonium salts are also sparingly soluble, but those of lithium or of certain organic bases (especially piperazine (p. 173) and lysidine (p. 73)) are freely soluble.

Uric acid was first characterized by Scheele in 1776. He found it to be the chief constituent of the "stones" sometimes

formed in the bladder, proved it was an acid, and discovered a characteristic test for it, the *murexide reaction.*

If uric acid is evaporated to dryness with nitric acid, a yellow substance is left which, with ammonia, gives a violet salt (*murexide*).

Some forty years later, Prout isolated *murexide* (the ammonium salt of *purpuric acid*) more definitely, and much later still it was shown to possess the formula $C_8H_{12}O_6N_6$, H_2O, and to be formed also when alloxan and uramil were mixed in ammoniacal solution. The free purpuric acid is, however, unstable.

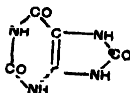
Prout also showed that, by oxidation of uric acid, alloxan was formed; whilst about the same time Wöhler noted that upon dry distillation uric acid gave ammonia, carbon dioxide, cyanuric acid, and urea. These preliminary observations were completed when Liebig and Mitscherlich determined the empirical formula, $C_5H_4N_4O_3$, and obtained by oxidation under different conditions, allantoin, urea, and alloxan.

The next contribution to the problem was by Baeyer and his students (1860-1870). He is mainly responsible for the knowledge of the mutual relations of the cyclic ureides discussed in the preceding section, and he also found that—

(*a*) Uric acid, heated with hydrochloric acid at 170°, gives ammonia, carbon dioxide, and glycocoll.

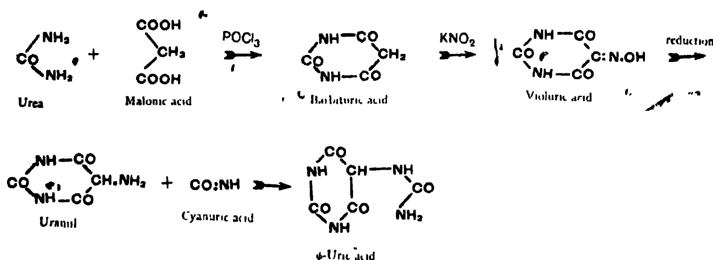
(*b*) Uric acid, oxidized by chlorine water, breaks up into alloxan and urea.

About 1870 Medicus discussed some twenty possible formulæ for uric acid, and summed up in favour of:

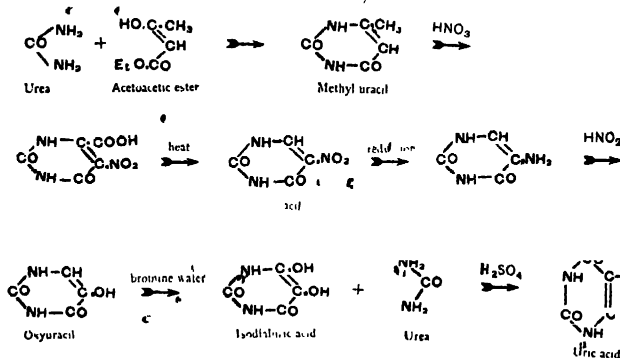


In the meantime Baeyer tried to apply the knowledge he had gained to a synthesis of uric acid, but only succeeded in obtaining a *pseudo-uric acid*, containing an extra molecule of water, which

he could not eliminate. The following are the steps of his synthesis :



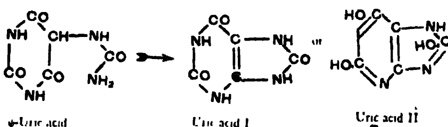
Horbaczewski next effected syntheses of uric acid itself (of little theoretical interest) by fusing up urea with glycocoll or substituted amino-acids. A more satisfactory synthesis was achieved in 1888 by Behrend and Roosen, who started from *methyl uracyl*:



At about this time E. Fischer turned his attention to the *purine* group, as he termed them (p. 190), and showed that their constitution could be determined by oxidation (with chlorine water), and methylation, and confirmed by synthesis.

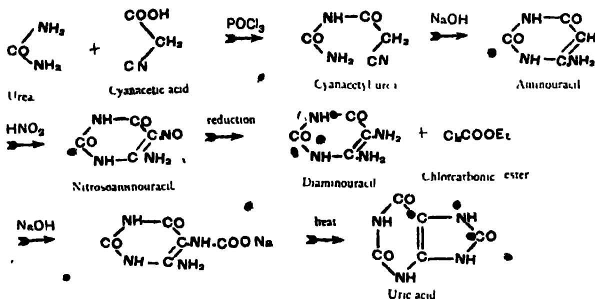
He found, for example, that by methylation of the lead or potassium salts of uric acid with methyl iodide, five mono-, six di-, four tri-, and one tetra-methyluric acids could be prepared,

in accordance with theory. He established the constitution of all these methylated acids by oxidation into different methyl alloxans and methyl ureas, and further supplied the last step in Baeyer's uric acid synthesis in 1896, when he found that ψ-uric or ψ-methyluric acids gave up one molecule of water when heated with anhydrous oxalic or hydrochloric acids, yielding the corresponding uric acids.



Moreover, whilst the methyl derivatives were shown in all cases to be *N*-ethers, he suggested that the acidic and heterocyclic nature of uric acid was better illustrated by the tautomeric structure II.

More recently (1901) W. Traube has furnished another kind of uric acid synthesis:



V. Other Purine Compounds

It remains to describe the nature of the remaining naturally occurring purines, and to this end we will consider three individual members, which are typical of the rest, namely, *caffeine*, *xanthine*, and *guanine*.

It may first be mentioned that Fischer employed the following general methods of analysis and synthesis:

I. *Analysis.*

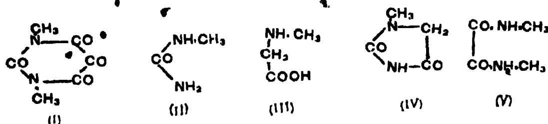
(i) When not previously known, he determined the number of *N*-methyl groups by the Zeisel method.
(ii) He examined the substituted *alloxan* and *urea* formed by the action of chlorine water on the purine compound.
(iii) He noted simpler (amino-acid) derivatives occurring in more profound decomposition of the purine ring-system.

II. *Synthesis.*

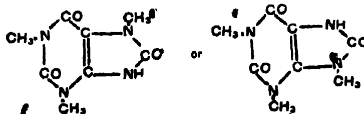
(i) He had previously obtained all the methyluric acids synthetically.
(ii) By the action of phosphorus oxychloride or pentachloride on these he replaced one or more hydroxyl groups by chlorine.
(iii) He next replaced the chlorine by other groups, or,
(iv) He reduced the chloropurines (replacement of Cl by H).

Thus, with *caffeine*, $C_8H_{10}O_2N_4$, a drug occurring in coffee, tea, and kola nuts, which crystallizes in slender needles, melting and subliming at 235°, he carried out the following series of experiments:—

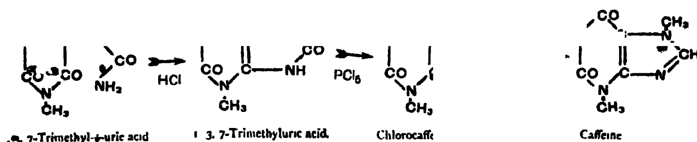
(i) It was shown to possess three methyl groups.
(ii) Mild oxidation yielded *dimethyl alloxan* (I) and *methyl urea* (II).
(iii) More vigorous decomposition furnished *methylglycocoll* (III), *methyl hydantoin* (IV), and *dimethyl oxamide* (V).



From the first four products, caffeine appears to be either

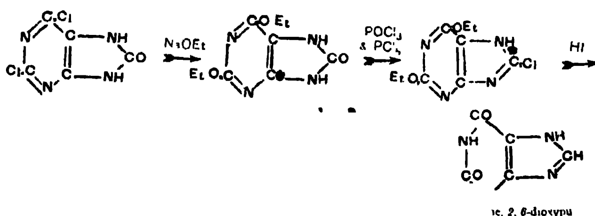


The fifth compound, dimethyloxamide, points definitely to the first of these, and this has been confirmed synthetically:

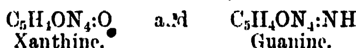


Xanthine, $C_5H_4O_2N_4$, resembles uric acid in many respects, both chemically and with regard to its occurrence in nature, but is both feebly basic and acidic. It contains no methyl groups, but by methylation yields *caffeine* and *theobromine* (see table below). Its oxidation products are notably urea, alloxan, and glycocoll.

Now, when uric acid (*trioxypurine*) is boiled with phosphorus oxychloride, a dichloro-oxypurine is produced, which on methylation yields 7.9-*dimethyluric acid*; consequently the dichloro derivative is 2.6-dichloro-8-oxypurine. From this synthetic compound *xanthine* has been synthesized as follows:—



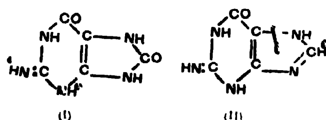
Guanine, $C_5H_5ON_5$, which occurs in guano, the pancreas, clover, beetroots, etc., is nearly related to xanthine, and the nature of its relationship may be guessed by comparing the formulæ:



$C_5H_4ON_4:O$ and $C_5H_4ON_4:NH$
Xanthine. Guanine.

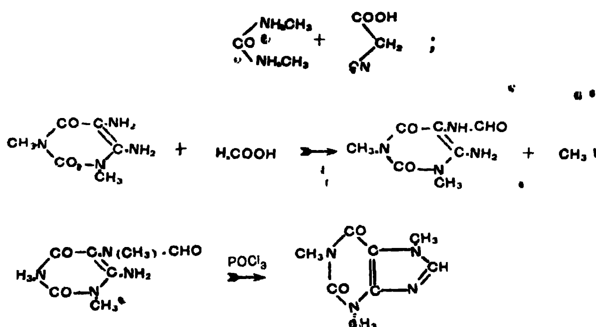
Moreover, since by the action of nitrous acid guanine is converted to xanthine, the supposition that guanine is the guanidine derivative corresponding to xanthine (from urea) is confirmed.

Now malonylguanidine (p. 195) condenses with urea to oxyguanine (I), and therefore guanine must be represented by II:

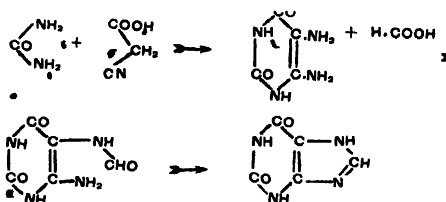


W. Traube has effected syntheses of the purines on lines analogous to those followed by him in the case of uric acid.

Caffeine.—From *sym*-dimethylurea and cyanacetic acid:



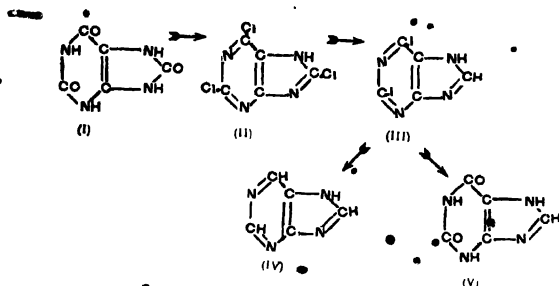
Xanthine.—From urea and cyanacetic acid:



Guanine was similarly prepared from guanidine and cyanacetic acid.

The parent substance of the whole series, *purine*, has not yet been found in nature, but Fischer has prepared it artificially by

converting *uric acid* (I) into *trichloropurine* (II), which by successive reduction with cold hydriodic acid and zinc dust in acetic acid furnishes *diiodopurine* (III) and *purine* (IV). On boiling the *diiodopurine* with hydrogen chloride, *xanthine* (V) is produced.



The table on the next page gives a summary of the more important natural compounds of this group :

	Formula.	*Chemical Name.*	*Discovery.*		*Occurrence.*
Uric acid.	$C_5H_4O_3N_4$	2.6.8-Trioxypurine.	1776	Scheele.	Muscles, urine, etc.
Xanthine.	$C_5H_4O_2N_4$	2.6-Dioxypurine.	1817	Marcet.	Animal secretions.
Guanine.	$C_5H_5ON_5$	2-Amino-6-oxypurine.	1844	Unger.	Guano.
Heteroxanthine.	$C_6H_6O_2N_4$	7-Methyl-2, 6-dioxypurine.	1885	Kossel.	Urine.
Theophylline.	$C_7H_8O_2N_4$	1.3-Dimethyl-2, 6-dioxypurine.	1888	Kossel.	Tea.
Theobromine.	$C_7H_8O_2N_4$	3.7-Dimethyl-2, 6-dioxypurine.	1842	Woskresorski.	Cocoa.
Paraxanthine.	$C_7H_8O_2N_4$	1.7-Dimethyl-2, 6-dioxypurine.	1883	Fischer.	Urine.
Caffeine, theine.	$C_8H_{10}O_2N_4$	1.3.7-Trimethyl-2, 6-dioxypurine.	1821	Pelletier.	Coffee. tea, etc.
Hypoxanthine.	$C_5H_4ON_4$	6-Oxypurine.	1850		Tea, potatoes, beetroot.
Adenine.	$C_5H_5N_5$	6-Aminopurine.	1885	Kossel.	Tea, beetroot, pancreas.

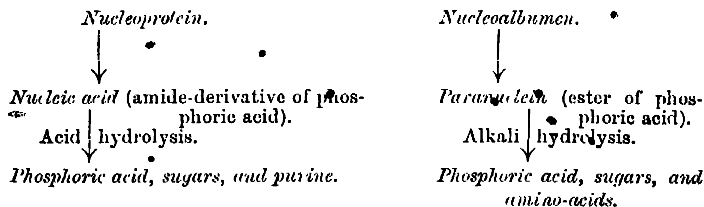
CHAPTER XI

THE POLYPEPTIDES

I. General

THE division of proteins into four main classes, according to the nature of their hydrolytic decomposition products, was referred to in the last chapter (p. 189), and attention was then focussed upon the *nucleoproteins*, which, when hydrolysed, yield phosphoric acid and purines. We must now take up the study of another of these classes, the *nucleoalbumens*, from which phosphoric acid and many different amino-acids are produced by similar hydrating agents.

The hydrolytic decomposition of the nucleoalbumens is distinguished in several ways from that of the nucleoproteins, and it may be well to compare the two reactions before proceeding further.



Whilst, then, the nucleoproteins are built up from the purines, and so contain a heterocyclic ring-system, the nucleoalbumens are derived from *α*-amino-acids, the latter, with one or two exceptions detailed in the next section, being purely aliphatic compounds.

We must next consider the stages in the hydrolysis of the

nucleoalbumens. It is now fairly certain that the amino-acids are not the direct decomposition products of the nucleoalbumen, but that an intermediate substance, belonging to the class of "paranucleins," always intervenes. The detection and characterization of this intermediate phase was by no means a simple task, owing to the difficulty of checking the hydrolytic action at the desired stage.

Now it will be recalled that the nucleoproteins break down first of all into a similar (and yet quite different) intermediate compound—a "nucleic acid."

The nucleic acids and paranucleins resemble each other in being derivatives of phosphoric acid, but whereas the former are readily further broken up by acid hydrolysis (and are amides of phosphoric acid, compare chap. x. p. 190), the latter are much more stable to acids than to alkalies, and are probably esters of phosphoric acid.

The separation and purification of the different aminoacids from a given nucleoalbumen is another difficult operation. We may illustrate this by Fischer's directions for the isolation of aminoacids from casein or milk albumen:

Half a kilogram of casein is first digested in the cold with one and a half litres of concentrated hydrochloric acid for an hour and a half. It is then heated at 100° for six hours, and saturated meanwhile with gaseous hydrogen chloride. After cooling, an equal volume of ice-cold alcohol is added, whereby a number of impurities are precipitated. The filtered solution now contains the aminoacids, formed by hydrolysis of the casein, in the form of the hydrochlorides of their esters.

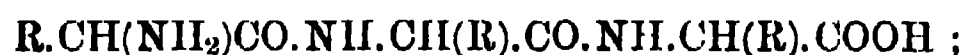
The solution is evaporated down in vacuo at 100° to a syrupy consistency, then redissolved in one and a half litres of absolute alcohol, and heated in a current of dry hydrogen chloride on the water-bath to complete the esterification.

After further purification the amino-acid esters are hydrolysed by exceedingly careful addition of alkali, and the free acids are finally extracted with ether. The ethereal extract is then fractionally distilled in vacuo and the different amino-acids finally purified by repeated fractionation.

The products so obtained are optically active, but may be racemized by heating with baryta for some time. In this way amino-acids identical with the "polypeptides" synthetically

produced in the laboratory by Fischer (as described in sections III and IV) have sometimes been isolated.

Preliminary work of the above type rendered it obvious that the ultimate form of the amino-acids present in the nucleo-albumens was a complex condensation product formed from a number of amino-acid radicles by successive elimination of the elements of water between the amino and hydroxyl groups present. For example:



$$R.CH(NH_2)CO.NH.CH(R).CO.NH.CH(R).COOH;$$

and Fischer then took up the detailed study of the synthesis of derivatives of this type, to which he gave the name *polypeptide*. The latter term, explicitly defined, refers to those substances formed by condensation of an amino with a hydroxyl group from two or more amino-acids. Similarly, a condensation product from two amino-acids is termed a *dipeptide*, from three, a *tripeptide*, and so on.

Before proceeding to an account of the more notable protein amino-acids, and of Fischer's synthetic production of polypeptides therefrom, we will glance at some attempts which are being made to determine the constitution of the proteins by analytic, rather than synthetic, means.

This side of the work is chiefly in the hands of Abderhalden (the synthetic methods, on the other hand, being due almost exclusively to Fischer and Curtius). Abderhalden endeavours to arrive at the structure of the nucleoalbumens by studying the products of partial hydrolysis. By separating and examining the intermediate products, it is possible to deduce the structure of the original complex by finding the manner in which the ultimate residues are linked in pairs or trios. Thus, *edestin*, a complex nucleoalbumen, gave three polypeptides on partial hydrolysis, one of which contained glutaric acid, tryptophane, and leucine, and the third tyrosine, glycine, and leucine.

Another interesting suggestion in this direction is the application of physical chemistry to the problem by Mathieu.

If the rate of hydrolysis of a protein by an acid is measured in the usual way, it is found that the speed of the

reaction does not always change regularly in accordance with the law of mass action. The abrupt changes of the rate of hydrolysis, found for example in the case of gelatine, are considered to mark definite stages of the hydrolysis.

Finally, although there is nothing but a superficial chemical connection between the two classes, it may be mentioned that a series of naturally occurring oxygen analogues of the polypeptides has recently come to light. The substances in question are natural vegetable acids, occurring in some of the Coniferæ, and have been given the generic name of "*etholides*"; they are derived from condensed hydroxy- (instead of amino-) acids, and possess the general structure:



$$R.CH(OH).[CH_2]_n.CO.O.CHR.[CH_2]_n.CO.O.CHR.[CH_2]_n.COOH.$$

II. The More Common Amino-Acids occurring in Polypeptides

It has just been stated that the ultimate products obtained from the proteins are in general a number of different amino-acids; the separation and purification of these is extremely difficult, owing to their close mutual chemical resemblance. However, the thorough investigations of the past twenty years have shown that most polypeptides are built up from the amino-acids enumerated below. It will be observed that all these are α-amino-acids, and that nearly all contain asymmetric carbon atoms, thus accounting for the optical activity displayed by so many natural polypeptides.

The ultimate amino-acids may be classified as follows:

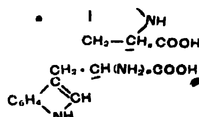
Monobasic aliphatic acids.

Glycocoll	Aminoacetic acid	$CH_2(NH_2).COOH$
Alanine	Methylglycocoll	$CH_3.CH(NH_2).COOH$
Serine	β-Hydroxyalanine	$CH_2(OH).CH(NH_2).COOH$
Cystine	α-Dithioalanine	$S_2[C(CH_3)(NH_2)COOH]_2$
Phenylalanine		$C_6H_5.CH_2.CH(NH_2).COOH$
Tyrosine	*p*-Oxyphenylalanine	$HO.C_6H_4.CH_2.CH(NH_2).COOH$
Leucine	α-Amino*iso*capronic acid	$(CH_3)_2.CH.CH_2.CH(NH_2).COOH$

Dibasic aliphatic acids.

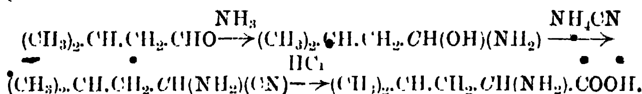
Asparagine	Aminosuccinamic acid	$NH_2.CO.CH_2.CH(NH_2).COOH$
Aspartic acid	Aminosuccinic acid	$COOH.CH_2.CH(NH_2).COOH$
Glutaminic acid	α-Aminoglutaric acid	$COOH.CH_2.CH_2.CH(NH_2).COOH$

Heterocyclic acids.

Proline	Pyrrolidine α-carboxylic acid	
Tryptophane	β-β-Indol-α-amino-propionic acid	$CH_2.CH(NH_2).COOH$ / C_6H_4 C CH NH

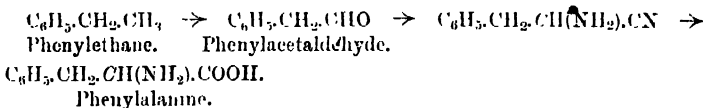
Several of the above acids are quite simple in structure; the synthetic production of the more complex members may be recalled here:

Leucine, from isovaleraldehyde and ammonium cyanide:

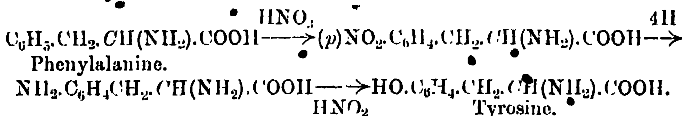


$$(CH_3)_2.CH.CH_2.CHO \xrightarrow{NH_3} (CH_3)_2.CH.CH_2.CH(OH)(NH_2) \xrightarrow{NH_4CN}$$
$$(CH_3)_2.CH.CH_2.CH(NH_2)(CN) \xrightarrow{HCl} (CH_3)_2.CH.CH_2.CH(NH_2).COOH.$$

Phenylalanine and *tyrosine*, from phenylacetaldehyde:



$C_6H_5.CH_2.CH_3 \rightarrow C_6H_5.CH_2.CHO \rightarrow C_6H_5.CH_2.CH(NH_2).CN \rightarrow$
Phenylethane. Phenylacetaldehyde.
$C_6H_5.CH_2.CH(NH_2).COOH.$
Phenylalanine.



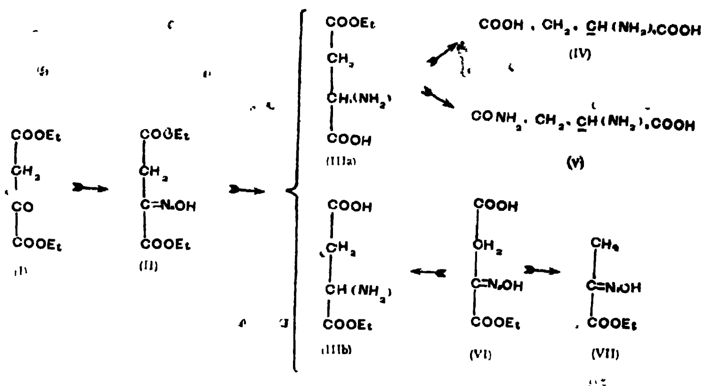
$$C_6H_5.CH_2.CH(NH_2).COOH \xrightarrow{HNO_3} (p)NO_2.C_6H_4.CH_2.CH(NH_2).COOH \xrightarrow{4H}$$
Phenylalanine.
$$NH_2.C_6H_4CH_2.CH(NH_2).COOH \xrightarrow{HNO_2} HO.C_6H_4.CH_2.CH(NH_2).COOH.$$
Tyrosine.

Aspartic acid and *asparagine*, from oxalacetic ester.

Oxalacetic ester (I), from the Claisen condensation of ethyl acetate and oxalate, yields an oxime (diethyl oximinosuccinate, II), which by reduction and semihydrolysis yields the two mono-ethyl esters of aminosuccinic acid (III*a* and III*b*).

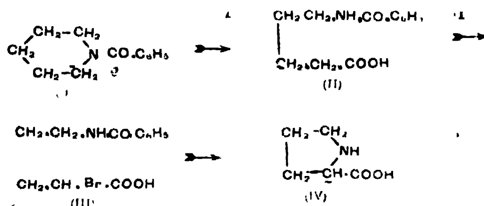
III*a*, on complete hydrolysis, yields $(d+l)$ *aspartic acid* (IV), or, with ammonia $(d+l)$, asparagine (V). On the other-hand, the ester-acid III*b* is also obtainable by reduction of monoethyl oximino-succinic acid (VI), which also gives the oxime of pyruvic ester (VII) when heated. Consequently the

orientations of aspartic acid and asparagine must be assigned as in formulæ IV and V (from III*a*).



Proline and tryptophane are two pyrrol derivatives found in the hydrolytic products of certain proteins, and were discovered much more recently than the rest of the amino-acids, namely, in 1899 (Fischer) and 1896 (Kossel) respectively.

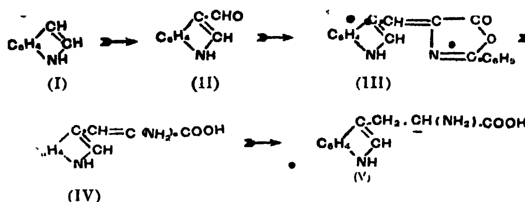
Proline has been synthesized by Fischer as follows : *N*-benzoyl-piperidine (I) is oxidized carefully by permanganate, whereby δ-benzoylamino-*n*-valeric acid (II) results ; on bromination this becomes α-bromo-δ-benzoylamino-*n*-valeric acid (III), which is converted by boiling with hydrochloric acid to *r*-proline (IV).



r-Tryptophane, the indol acid, was synthetically produced as follows by Ellinger in 1907 :

Indol (I) is first heated with chloroform and caustic potash (Reimer's reaction), whereby indol β aldehyde (II) is formed. This is condensed with hippuric acid in presence of dilute alkali, when the deeply coloured substance III, an " *azlactone*," is produced in accordance with the usual

behaviour of hippuric acid to aromatic aldehydes. Azlactones, however, are decomposed by hot alkali, with rupture of the lactone ring and saponification of the benzoyl group. The substance III in question is accordingly, by this treatment, converted to the open-chain acid (IV), which may be reduced to the acid V, identical with racemic tryptophane.

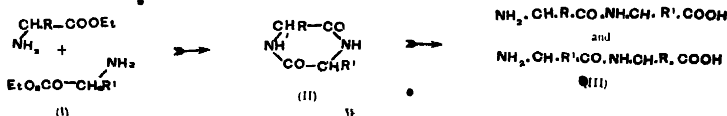


III. Fischer's Synthetic Methods for the Production of Polypeptides

In the course of the classical work which is still being prosecuted by Emil Fischer, in accordance with the plan outlined in Section I (p. 207) of this chapter, that chemist has elaborated five distinct methods for preparing polypeptide derivatives. We will describe these in the chronological order in which Fischer devised them, and at the same time compare the applicability and fertility of each type.

First Method.—Elimination of alcohol between two molecules of amino-acid esters.

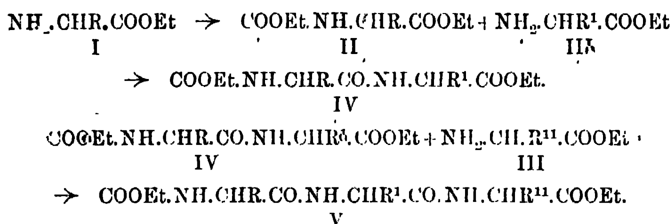
This is effected by heating the mixture of esters (I) in sealed tubes at 170 , when a heterocylic compound (a reduced derivative of *pyrazine*, p. 172) is formed (II). By careful treatment of this product with hydrochloric acid, one molecular proportion of water is added, and a *dipeptide* (III) results.



Second Method.—The first method permits the interaction of the amino groups in each of the amino-esters, but, if the composition of the end product is to be governed with certainty, it is necessary to control the reaction so that only a specific and

chosen amino-group may be free to condense. Fischer's subsequent methods, therefore, were concerned with artifices to secure this end, and with improvements in the yield of the final products. His second method does not afford very good yields of the polypeptides, but is useful as a method of controlling the synthesis.

An amino-ester (I) is first treated with ethyl chlorcarbonate, whereby the substance (II) is produced, and the amino group present in (I) "protected" against further condensation. The product II is then heated as before with another amino-ester (III) in sealed tubes for two or three days, and the product (IV) carefully hydrolysed, when a *dipeptide* again results. Or, the process may be repeated indefinitely with the polypeptide ester (IV), leading to *tri-*, *tetra-*, or *pentapeptides* (V).



$NH_2.CHR.COOEt \rightarrow COOEt.NH.CHR.COOEt + NH_2.CHR^1.COOEt$
I — II — III

$\rightarrow COOEt.NH.CHR.CO.NH.CHR^1.COOEt.$
IV

$COOEt.NH.CHR.CO.NH.CHR^1.COOEt + NH_2.CH.R^{11}.COOEt$
IV — III

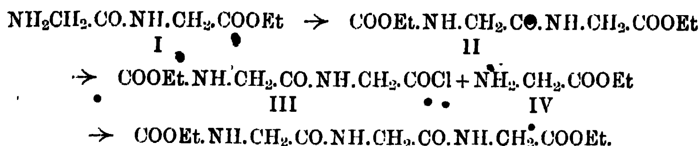
$\rightarrow COOEt.NH.CHR.CO.NH.CHR^1.CO.NH.CHR^{11}.COOEt.$
V

Hence, whereas the first method only gives *dipeptides*, the above can give derivatives of higher polypeptides of known and pre-determined constitution. However, the final products are not true polypeptides, but contain in addition the carbethoxyl-imino group COOEt.NH-, which cannot be removed without breaking down the whole molecule.

Third Method.—The next modification also gives carbethoxyl derivatives of the polypeptides, but the yields are much improved, owing to the final condensation being carried out between an acid chloride and an amino-group; so that hydrogen chloride, instead of alcohol, is eliminated.

The amino-ester in which the amino-group is not desired to suffer condensation (I), is "protected" as before by treatment with ethyl chlorcarbonate, forming the carbethoxyl derivative (II). On adding *one* molecular proportion of thionyl chloride to this ester, only the carbethoxyl group of the

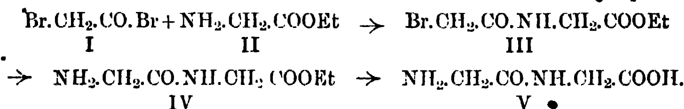
terminal radicle $-NH.CH_2.COOEt$ is converted to an acid chloride (III), which is then heated with the required amino-ester (IV):—



$$NH_2CH_2.CO.NH.CH_2.COOEt \rightarrow COOEt.NH.CH_2.CO.NH.CH_2.COOEt$$
$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$
$$\rightarrow COOEt.NH.CH_2.CO.NH.CH_2.COCl + NH_2.CH_2.COOEt$$
$$\text{III} \qquad\qquad\qquad\qquad \text{IV}$$
$$\rightarrow COOEt.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.COOEt.$$

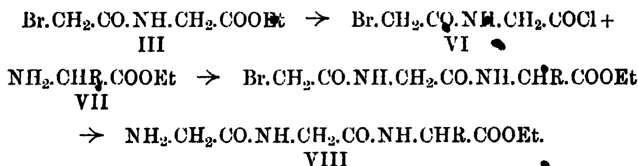
Fourth Method.—Fischer's next improvement was a simple device by means of which true polypeptides of any desired configuration could be obtained; the preliminary condensation was effected between an amino-ester and bromacetyl bromide, and subsequently the bromacyl group was converted to the glycyl residue by interaction with ammonia.

Thus, starting from bromacetyl bromide (I) and glycocoll ester (II), the ester (III) is obtained, and, on treatment with alcoholic ammonia, passes readily into glycylglycine ester (IV), which can be hydrolysed to glycylglycine (V).



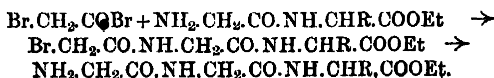
$$Br.CH_2.CO.Br + NH_2.CH_2.COOEt \rightarrow Br.CH_2.CO.NH.CH_2.COOEt$$
$$\text{I} \qquad\qquad \text{II} \qquad\qquad\qquad \text{III}$$
$$\rightarrow NH_2.CH_2.CO.NH.CH_2.COOEt \rightarrow NH_2.CH_2.CO.NH.CH_2.COOH.$$
$$\text{IV} \qquad\qquad\qquad\qquad \text{V}$$

On the other hand, the bromo-ester (III) may be warmed with a molecular proportion of thionyl chloride (as in the third method), the resulting acid chloride (VI) condensed further with a fresh amino-ester (VII), and then treated with alcoholic ammonia:



$$Br.CH_2.CO.NH.CH_2.COOEt \rightarrow Br.CH_2.CO.NH.CH_2.COCl +$$
$$\text{III} \qquad\qquad\qquad\qquad \text{VI}$$
$$NH_2.CHR.COOEt \rightarrow Br.CH_2.CO.NH.CH_2.CO.NH.CHR.COOEt$$
$$\text{VII}$$
$$\rightarrow NH_2.CH_2.CO.NH.CH_2.CO.NH.CHR.COOEt.$$
$$\text{VIII}$$

Or, again, the polypeptide esters (IV) or (VIII), when obtained, may be resubmitted to the action of bromo-acetyl bromide, and fresh condensations effected at the "amino-end" of the molecule:

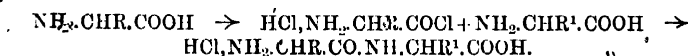


$$Br.CH_2.CO.Br + NH_2.CH_2.CO.NH.CHR.COOEt \rightarrow$$
$$Br.CH_2.CO.NH.CH_2.CO.NH.CHR.COOEt \rightarrow$$
$$NH_2.CH_2.CO.NH.CH_2.CO.NH.CHR.COOEt.$$

As might be expected, this method has proved the most fruitful of all, and the most complex synthetic polypeptide yet prepared (an *octadecapeptide* containing fifteen glycyl and three leucyl residues) was obtained by repeated application of this method.

Fifth Method.—There remains one other type of synthesis worthy of notice, but of less extended application than the preceding.

Certain amino-acids, on careful application of a mixture of acetyl chloride with some phosphorus pentachloride, yield the hydro-chloride of the amino-acid chloride; this can in turn be directly condensed with other amino-acids.



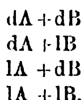
$NH_2.CHR.COOH \rightarrow HCl,NH_2.CHR.COCl + NH_2.CHR^1.COOH \rightarrow HCl,NH_2.CHR.CO.NH.CHR^1.COOH.$

IV. The Synthesis of Optically Active Polypeptides

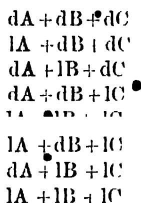
The compounds formed according to the above schemes resemble the natural protein derivatives in their physical appearance, their bitter taste, and their chemical reactions (formation of biuret on heating, and of characteristic precipitates, with the usual albumen reagents, such as phosphotungstic acids). If, however, racemic amino-esters have been employed throughout, the products are of course optically inactive, and it remains to give some indication of the methods employed in the preparation of those polypeptides which carry their resemblance to the natural substances, even to the extent of showing optical activity.

Such compounds have most frequently been synthesized from optically active amino-acids, the actual resolution of the racemic form of the molecule being thus effected before the synthetic process commenced. The reason for this course is that a polypeptide contains in general as many asymmetric carbon atoms as there are peptide groups; hence, if from two racemic amino-

acids, A and B, we build up the dipeptide AB, we encounter the possibility of the following *four* acids in the product:


dA + dB
dA + lB
lA + dB
lA + lB.

Similarly, in synthesizing a tripeptide ABC from the racemic amino-acids A, B, and C, we should obtain a mixture of *eight* optical isomerides as follows:


dA + dB + dC
lA + dB + dC
dA + lB + dC
dA + dB + lC
[illegible]
lA + dB + lC
dA + lB + lC
lA + lB + lC

And, in general terms, a polypeptide possessing *n* peptide groups and synthesized from *n* different amino-acids will contain 2^n different optical isomers.

Resolution of so complicated a mixture by fractional crystallization of the salts of the racemic peptide with some optically active base is obviously hopeless; and, indeed, this method, sufficiently tedious under the happiest of circumstances, is further invalidated in this case by the exceedingly feebly acidic character of the polypeptides.

Fischer therefore confined his efforts to obtaining the simple amino-acids themselves in the optically pure state, and to this end employed both the fermentation and the fractional crystallization methods:

(*a*) *Treatment of a racemic amino-acid with an enzyme.*—When certain racemic amino-acids are subjected to the action of the pancreatic or other enzyme, one active form is frequently destroyed in preference to the other, in accordance with the usual behaviour of enzymes to asymmetric systems. The action of the enzyme, however, is very largely conditioned by the nature of the groups surrounding the asymmetric carbon atom, and therefore cannot be depended upon.

(*b*) *Fractional crystallization of the salts of the racemic amino-acid with brucine or strychnine.*—As already mentioned, this plan also presents difficulties, owing to the feeble capacity for salt formation of the amphoteric amino-acid radicle.

Fischer overcame this obstacle, however, by increasing the acidity of the amino-acid through acylation. The acid was first of all transformed to its *N*-benzoyl, *N*-benzenesulphonyl, or *N*-naphthalenesulphonyl derivative:



$$R.CH(NH_2).COOH \rightarrow R.CH(NH.CO.C_6H_5).COOH.$$

The latter compounds readily yield salts with brucine or strychnine, and by fractional crystallization the salts were separated into those of the pure optical antipodes.

The acids recovered from the optically active pure salts were then employed by Fischer in the synthetic processes to which attention has already been paid.

CHAPTER XII

THE CARBOHYDRATES: GENERAL CHARACTERISTICS AND REACTIONS

I. Classification and Nomenclature

We have been concerned in the past chapters with naturally occurring organic substances of a nitrogenous nature, belonging to both closed-chain (heterocyclic) and open-chain series; with the present chapter we commence a review of the equally important class of compounds grouped under the term "carbohydrates." These contain only the elements of carbon, hydrogen, and oxygen, and are essentially aliphatic, non-cyclic compounds (except in a few cases, considered separately in chap. xiv.; and in certain lactone-like modifications, which will likewise receive notice later). The empirical composition of all carbohydrates, furthermore, is very simple and uniform, and may be represented as $C_m(H_2O)_n$.

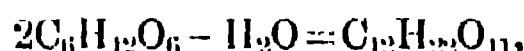
Numerous representatives of this class occur in both the animal and the vegetable worlds, especially in the latter; typical examples are *glucose* or *grape-sugar*, $C_6H_{12}O_6$, found in honey and in many fruits; *cane-sugar*, $C_{12}H_{22}O_{11}$, from sugar cane and beet; *starch* $[C_6H_{10}O_5]_x$; and *cellulose* or *wood-fibre* $[C_{12}H_{20}O_{10}]_x$.

The numerical relations found to exist between the atomic proportions of carbon and of water in a carbohydrate molecule has led to a means of classification for the whole series. Thus we see that *glucose* is $C_6(H_2O)_6$, *cane-sugar*, $C_{12}(H_2O)_{11}$, *starch*, $[C_6(H_2O)_5]_x$, and *cellulose* $[C_{12}(H_2O)_{10}]_x$, the exact molecular complexity of the two last being unknown, but very considerable.

The simplest of the above compounds is therefore *glucose*, in which the number of carbon atoms and of (H_2O) groups is equal; this fact serves as the basis of the general classification of the

carbohydrates, and such compounds are termed *monosaccharides*, the appellation *saccharide* denoting a carbohydrate.

In the next place, *cane-sugar* contains one molecule of water less than two molecules of glucose:



$$2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11},$$

and this furnishes a means of correlating the more complicated members of the group.

The complete fundamental nomenclature assigned to the carbohydrates is thus as follows:—

MONOSACCHARIDES: *Carbohydrates of the general formula*, $C_m(H_2O)_m$.

DISACCHARIDES: *Carbohydrates of the general formula*, $C_{2m}(H_2O)_{2m-1}$; these may be regarded, for the moment, as derived from two molecules of the same or of different *monosaccharides* by elimination of one molecule of water.

TRISACCHARIDES: *Carbohydrates of the general formula*, $C_{3m}(H_2O)_{3m-2}$; by elimination of two molecules of water from three *monosaccharides*.

TETRASACCHARIDES: *Carbohydrates of the general formula*, $C_{4m}(H_2O)_{4m-3}$; etc.

POLYSACCHARIDES: Complex polymerized bodies of the general formula $[C_m(H_2O)_n]_x$; practically speaking, it may be said that in all cases $m = 6$ and $n = 5$.

To the latter class belong the starches and gums found in the vegetable kingdom, and also cellulose, whilst the former classes comprise what are more generally termed the "sugars."

We shall be restricted almost entirely to the discussion of the *sugars*, and here, as in the polysaccharides, the most important natural compounds possess the formula $C_6(H_2O)_6$, or are condensation products from two or more $C_6H_{12}O_6$ (monosaccharide) molecules.

There are, however, a number of interesting substances of the general formulæ, $C_2H_4O_2$, $C_3H_6O_3$, $C_4H_8O_4$, $C_5H_{10}O_5$, $C_7H_{14}O_7$,

$C_8H_{16}O_8$, and $C_9H_{18}O_9$, and we have now to extend the classification in detail so as to differentiate between these.

Such compounds are, by the preceding definition, *monosaccharides*, and they are distinguished according to the number of carbon atoms each possesses, a prefix indicating this number being added to the generic termination *-ose*.*

Finally, as will be shown below, some monosaccharides are *aldehydic*, others *ketonic*, in nature; and again, in a few cases, homologous *methyl* derivatives of the sugars are known. This is allowed for in the nomenclature by a further prefix indicating the type of the monosaccharide in question. For example, glucose is an *aldohexose*, fructose a *ketohexose*, and rhamnohexose a *methylhexose*. These subdivisions will be best appreciated if we draw up a classified table of the carbohydrates which will be described in this and the following chapters :—

MONOSACCHARIDES, $C_m(H_2O)_m$	(*Monoses*, CH_2O)	(Formaldehyde).
	Dioses, $C_2H_4O_2$	Glycollic aldehyde.
	Trioses, $C_3H_6O_3$	
	Aldotriose	Glycerose.
	Ketotriose	Dioxyacetone.
	Methyltriose	Methylglycerose.
	Tetroses, $C_4H_8O_4$	
	Aldotetroses	Erythrose and threose.
	Pentoses, $C_5H_{10}O_5$	
	Aldopentoses	Arabinose, xylose, lyxose, and ribose.
	Methylpentoses	Rhamnose and isorhamnose.
	Hexoses, $C_6H_{12}O_6$	
	Aldohexoses	Glucose, mannose, galactose.
	Ketohexoses	Fructose, sorbinose, formose.

* The suffix *-ose* was formerly (and is sometimes at present) used indiscriminately for the "condensed" sugars (di-, tri-, etc., saccharides), as well as for the individual monosaccharides. This tends to confusion, however, since by this system *monose*, *diose*, and *triose* (at least) refer to two different classes.

	Methylhexoses .	Rhamnohexose.
	Heptoses, $C_7H_{14}O_7$	
	Aldoheptoses .	Glucoheptose and mannoheptose.
	Ketoheptoses .	Fructoheptose.
	Methylheptoses .	Rhamnoheptose.
DISACCHARIDES, $C_{2m}(H_2O)_{2m-1}$	*Pentose derivatives* .	Arabiose.
	Hexose derivatives .	Cane-sugar, maltose, lactose, and melibiose.
TRISACCHARIDES, $C_{3m}(H_2O)_{3m-2}$	*Pentose derivatives* .	Rhamninose.
	Hexose derivatives .	Raffinose.
POLYSACCHARIDES, $[C_m(H_2O)_n]_x$	...	Starch, dextrin, gum arabic, cellulose.

II. GENERAL CHEMICAL BEHAVIOUR OF THE CARBOHYDRATES

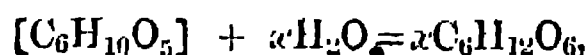
The carbohydrates are sharply divided into two classes from the point of view of their chemical reactions:—

(i) The *monosaccharides*.

(ii) The rest of the saccharides.

The distinctive feature of the second class is that they are, more or less readily, broken down hydrolytically by various agents into mixtures of monosaccharides.

Thus the starches and gums, when boiled with dilute acids, furnish the simpler saccharides according to the equation:



$$[C_6H_{10}O_5] + xH_2O = xC_6H_{12}O_6,$$

or, more generally,



$$[C_m(H_2O)_n]_x + xyH_2O = xC_m(H_2O)_m,$$

where

$$n = m - y.$$

The di- and tri-saccharides behave similarly, and as a rule these and the polysaccharides are also susceptible to the action of various ferments, living or unorganized (enzymes). The ferments are, however, selective in their attack; a given disaccharide, for example, will respond to the action of invertase,

but not to that of emulsin. The rules governing the selective propensities of the various ferments are referred to later (chap. xv., p. 289).

Further reference to the specific behaviour of the polysaccharides is unnecessary, since the subsequent reactions are invariably those of the monosaccharides formed by hydrolysis, except in the case of violent reagents, which behave with the polysaccharides similarly to their deportment with the monosaccharides. Thus strong sulphuric acid exerts a charring effect upon all carbohydrates, carbon, oxides of carbon, water, acrolein, and various other simple products resulting; and concentrated nitric acid oxidizes all the members of the class, firstly to oxydicarboxylic acids corresponding to the monosaccharides, and ultimately to oxalic acid and carbon dioxide.

Under suitable conditions, however, the starches and gums can be nitrated, and the polynitrocompounds (or rather nitrates) so formed are explosives of much technical importance (*cf.* p. 311).

The *monosaccharides*, on the other hand, are characterized by a series of reactions which are of the utmost importance, not only for their detection and estimation, but also in obtaining a knowledge of their mutual relations and individual structure.

Taking first of all those members in which an aldehydic group occurs (the *aldoses*), we are met by the following varieties of reactions:—

I. *Reduction.*

(*a*) In presence of sodium amalgam, the aldoses are converted into *normal hexahydric alcohols* of the general formula, $H_2[CH(OH)]_n$.

II. *Oxidation.*

(*a*) Mild oxidizing agents, such as bromine water (nascent hypobromous acid) or Fehling's solution (an alkaline solution of copper sulphate and Rochelle salt—potassium sodium tartrate), convert the aldoses to *monobasic acids*, the aldehyde group undergoing oxidation.

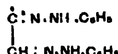
(*b*) With stronger oxidants, *dibasic acids* are produced, an alcoholic residue suffering oxidation as well as the aldehyde part of the molecule.

III. *Reactions of the aldehyde group.*

(*a*) With hydroxylamine, *oximes* are produced.

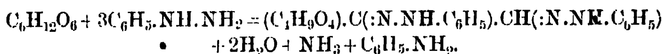
(*b*) With prussic acid, the usual *addition compounds* (nitriles of oxy-acids, characteristic of aldehydes) are formed.

(*c*) With phenylhydrazine, the first product is a *phenylhydrazone* of the usual type, $R.CH:N.NH.C_6H_5$; in presence of excess of the warm reagent, however, a further change takes place, and an alcoholic group —CH(OH)— is oxydized to carbonyl, which at once condenses with more phenylhydrazine to produce a compound of the general formula,



which is known as an *osazone*.

The complete process in the case of an aldohexose is thus:



$$C_6H_{12}O_6 + 3C_6H_5.NH.NH_2 = (C_4H_9O_4).C(:N.NH.C_6H_5).CH(:N.NH.C_6H_5) + 2H_2O + NH_3 + C_6H_5.NH_2.$$

The *osazones*, which are much better crystallized than the *phenylhydrazones* of the sugars, yield the unstable *osones*, R.CO.CHO, when boiled with dilute acids, and the latter compounds are readily reducible to *ketoses*, $R.CO.CH_2(OH)$.

IV. *Reactions of the alcoholic groups.*

(*a*) Boiling acetic anhydride leads to the formation of *polyacetyl derivatives*, each free hydroxyl group being acetylated.

(*b*) Similarly, benzoylchloride reacts with monosaccharides to give *polybenzoyl derivatives*.

(*c*) *Ethereal substances* are readily produced by interaction with other alcohols, other monasaccharides, acids, or other classes of compounds.

The condensation products with other monosaccharides are the *di-*, *tri-*, etc., *saccharides*, whilst the remaining compounds form the group of *glucosides* (chap. xvi., p. 297), both *synthetic* and *naturally occurring*.

(*d*) *Salt-like compounds* are produced from aldoses in presence of calcium and strontium hydroxides.

The *ketoses* resemble the aldoses in chemical behaviour for the most part, but in certain important points are dissimilar:

I. *Reduction.*

(*a*) As with the aldoses, alkaline reduction leads to the formation of *normal hexahydric alcohols*.

II. *Oxidation.*

(*a*) Here the ketoses are differentiated from the aldoses, for two acids are always formed upon oxidation, the molecule being broken at the carbonyl group.

(It will be observed that this is merely the characteristic behaviour of simple aldehydes and ketones upon oxidation; aldehydes yield acids with the same number of carbon atoms; ketones yield a mixture of two acids, the sum of the carbon atoms in which is equal to the number present in the molecule of the original ketone.)

III. *Reactions of the ketonic group*, and

IV. *Reactions of the alcoholic group*.

These are analogous, generally speaking, to the transformations of the aldoses.

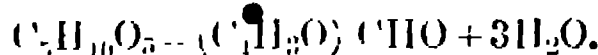
Thus, ketoses yield *oximes*, *oxynitriles*, *phenylhydrazones*, and *osazones* respectively with hydroxylamine, hydrocyanic acid, and phenylhydrazine; whilst the alcholic groups lead to *acetyl-* and *benzoyl-*compounds, *ethers* (*glucosides* or *polysaccharides*) and *salts* (with lime or strontia) as above.

The reactions of *methyl aldoses* and of *methyl-ketoses* correspond strictly with those of the simple aldoses and ketoses.

The following more individual reactions of the monosaccharides are also notable:

On prolonged boiling of a *hexose* with a dilute mineral acid, *levulinic acid*, $CH_3.CO.CH_2.CH_2.COOH$, is always found in the reaction mixture.

On the other hand, distillation of a *pentose* with concentrated hydrochloric acid, always produces *furfuraldehyde* (p. 45) in quantitative yield:



$$C_5H_{10}O_5 = (C_4H_3O).CHO + 3H_2O.$$

Pentoses may be recognized qualitatively by boiling their dilute aqueous solution with a few drops of strong hydrochloric acid, and then cooling the solution. If *phloroglucinol* is now added, a cherry-red colour appears on warming; whilst if *orcinol* be substituted for phloroglucinol, the colour is first red, then violet, and finally bluish-green. This test depends, of course, on the intermediate formation of furfuraldehyde.

A general reaction for sugars, starches, glucosides, and similar compounds is "*Molisch's Test*"; this consists in adding two drops of an alcoholic solution of α-naphthol and then excess of concentrated sulphuric acid to the solution of the carbohydrate. On warming and shaking, a reddish-violet colouration is produced, and when the mixture is poured into water, a bluish-violet precipitate results, which dissolves in alkalies, alcohol, or ether to a yellow solution.

It may be also recollected that the *osazones*, when condensed with aromatic *ortho*diamines, yield compounds of the *quinoxaline* series (chap. ix., p. 173).

III. THE GENERAL CHEMICAL NATURE OF THE MONOSACCHARIDES

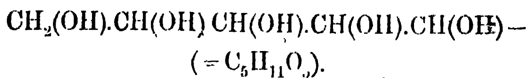
In the preceding section it was more or less tacitly assumed that the sugars were of an alcohol-aldehyde or alcohol-ketone nature; it will be helpful, perhaps, to indicate from a historical point of view how this knowledge of their general type of structure was acquired.

The structural chemistry of the sugar group dates, not unnaturally, only from the period when the capacity of carbon, not only to behave as a quadrivalent element, but to form compounds containing complex chains of carbon atoms, was first maintained by Kekulé in 1857; and again, at that period almost the only individual sugars definitely recognized were *cane-sugar*, $C_{12}H_{22}O_{11}$, and its two products of hydrolytic decomposition, *glucose*, $C_6H_{12}O_6$, and *fructose*, $C_6H_{12}O_6$.

We will consider the case of glucose somewhat in detail. In 1860, Berthelot drew attention to its capacity for forming ether-like derivatives (the glucosides, which yield glucose and other products by a simple hydrolytic process), and he suggested that it was a hexahydric alcohol, $C_6H_6(OH)_6$, in view of the production of what he believed to be glucose hexacetate (or hexa-acetylglucose).

Careful analytical examination showed that the last-named substance only possessed five acetyl groups, so that the composition of glucose was $C_6H_7O(OH)_5$, corresponding to a pentahydric alcohol.

It was soon seen that this conception implied a residue of one atom each of carbon, hydrogen, and oxygen being left, after allowance was made for a saturated pentahydric alcohol chain:



$$CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH)-$$
$$(= C_5H_{11}O_5).$$

The reducing properties of glucose towards alkaline silver and

copper solutions supported the natural conclusion that these atoms were combined as an aldehyde group $-\mathrm{C}\begin{smallmatrix}\diagup \mathrm{H}\\ \diagdown \mathrm{O}\end{smallmatrix}$, and in 1862 Berthelot definitely asserted that glucose was a (pentahydric) alcohol-aldehyde. Other chemists were loth to accept this view, on the grounds that certain reactions characteristic of aldehydes were not shown by glucose; in particular it did not unite additively with sodium bisulphite. Zincke, who had investigated ketone-alcohols containing the grouping $-\mathrm{CO.CH(OH)}-$, remarked that these were strongly reducing bodies (in contrast to ordinary ketones), whilst they did not yield sodium bisulphite compounds, and suggested that glucose was more nearly analogous to these than to an aldehyde, and that it was, in fact, a (pentahydric) alcohol-ketone.

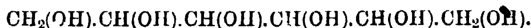
Others disputed whether the six carbon atoms present were cyclic, or formed a normal or a branched chain, and the subject was attacked by many workers until, in 1870, the present accepted formula for glucose was put forward independently by Baeyer and by Fittig:—



$$\mathrm{CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH).CHO}.$$

The main experimental bases on which this formula rested was as follows:—

(*a*) By alkaline reduction, glucose yielded the hexahydric alcohol *sorbitol*, $\mathrm{C_6H_8(OH)_6}$, which, by reduction with fuming hydriodic acid, formed *normal secondary hexyl iodide*, $\mathrm{CH_3.CH_2.CH_2.CH_2.CHI.CH_3}$, of known constitution. The carbon chain in glucose was therefore non-cyclic and normal, and the formula of *sorbitol* was:



$$\mathrm{CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH).CH_2(OH)}.$$

(*b*) Gentle oxidation of glucose gave *gluconic acid*, $\mathrm{C_5H_6(OH)_5.COOH}$, which, on ultimate reduction with hydriodic acid, produced *n-hexoic acid*, $\mathrm{CH_3.[CH_2]_4.COOH}$.

(*c*) More violent oxidation of glucose, or further oxidation of gluconic acid, produced a dibasic acid, *saccharic acid*, $\mathrm{COOH.[CH.(OH)]_4.COOH}$, which by ultimate reduction gave *a-adipic acid*, $\mathrm{COOH.[CH_2]_4.COOH}$.

These reactions show that the six-membered normal carbon chain persists undivided throughout the course of oxidation, so

that the carbonyl group present must be in the form of an *aldehyde*, $-CHO$.

Accordingly the Baeyer-Fittig formula becomes obvious.

On the other hand, *fructose* does not yield an acid containing six carbon atoms when oxidized, but a mixture of a four carbon-atom and a two carbon-atom acid (*trioxybutyric acid*, $CH_2(OH).CH(OH).CH(OH).COOH$, and *glycollic acid*, $CH_2(OH).COOH$). Nevertheless, by reduction of fructose, *sorbitol* and an isomeric normal-chain alcohol *mannitol* are formed, so that this sugar also possesses the normal six-membered chain of carbon atoms.

These facts led Kruseman (1876), Kiliani (1881), and Zincke (1883) to the view that fructose was of a ketonic nature, and since, as was pointed out by Kiliani, the addition-product of prussic acid and fructose can be hydrolysed to an acid which reduces ultimately to *methyl-n-butylacetic acid*,



$$CH_3.CH_2.CH_2.CH_2.CH(COOH).CH_3,$$

it follows that fructose is



$$CH_2(OH).CH(OH).CH(OH).CH(OH).CO.CH_2(OH).$$

The manner in which glucose and fructose are condensed to produce cane-sugar was not definitely settled until comparatively recently, and we will leave further discussion of the problem to an ensuing chapter.

Several monosaccharides other than glucose or fructose were soon discovered or added to those already known, some of which were found to possess the formula $C_5H_{10}O_5$ (*i.e.* were *pentoses*), whilst others were *hexoses* of an aldehydic nature.

Now, at about this period (1860-1875) the nature of optical activity in carbon compounds was attracting much notice, and in 1873 Le Bel and van't Hoff published their well-known theories connecting this property with the presence in a molecule of one or more "asymmetric carbon atoms." The formula of glucose,



$$CH_2(OH).\mathit{C}H(OH).\mathit{C}H(OH).\mathit{C}H(OH).\mathit{C}H(OH).CHO,$$

demands the presence of *four* asymmetric carbon atoms, and accordingly this would explain the existence of a number of

compounds isomeric and almost identical in chemical behaviour with glucose, but possessing different physical properties and widely varying rotatory powers.

The work on the sugars, therefore, subsequent to about 1875, is largely devoted to solving the intricate problem of the particular molecular configuration corresponding to each monosaccharide.

It is necessary to devote a separate chapter to a full description of the means whereby the desired end has been satisfactorily attained, and, beyond mentioning that, as in the cases of the purines (chap. x) and the polypeptides (chap. xi) the accomplishment of this somewhat appalling task is very largely due to Emil Fischer, we shall not in this section proceed beyond an enumeration of the general methods adopted.

It is well to appreciate the fact, in passing, that the constitutional formulæ of the aldohexoses and ketohexoses were proved simply by means of the above-mentioned reactions of reduction and oxidation, gentle and vigorous.

Subsequent to the date when these structures were settled, a number of the other important reactions were worked out, which proved essential to the further attack upon the molecular configuration of the members of the various classes of optically-active monosaccharides.

The chief of these are:—

(i) The condensation of the carbonyl group $-CO-$ with phenylhydrazine, producing *phenylhydrazones* (E. Fischer, 1877).

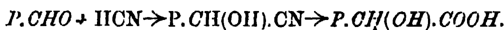
(ii) The extension of this reaction in the cases of sugars to the production of *osazones* (p. 222; E. Fischer, 1884).

(iii) The interaction of the carbonyl group $-CO-$ with hydroxylamine, yielding *oximes* (Victor Meyer, 1882).

(iv) *Transition from one series of monosaccharides to the next higher* (*e.g.* from a *pentose* to a *hexose*).

This was first carried out by Kiliani in 1885-1886, by means of the addition-product of an aldose with hydrogen cyanide. Using P- to represent the residue $CH_2(OH).[CH(OH)]_3-$ in a pentose, we see that the oxy-acid

resulting from hydrolysis of the above product will be produced according to the scheme:



$$P.CHO + HCN \rightarrow P.CH(OH).CN \rightarrow P.CH(OH).COOH.$$

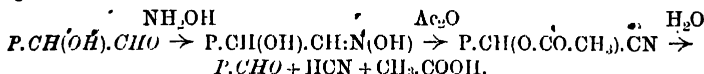
The acid so formed readily yields a lactone with the hydroxyl group attached to the γ-carbon atom in the chain, and alkaline reduction of this lactone produces a new oxy-aldehyde, P.CH(OH).CHO.

It will be seen that another asymmetric carbon atom has now been added, and, as a matter of fact, in many cases two physically different oxy-acids, P.CH(OH).COOH, are produced by this reaction.

(v) *Transition from one series of monosaccharides to the next lower (e.g.* from a *hexose* to a *pentose).*

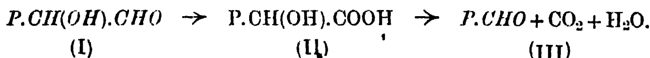
Two methods are available here:

(*a*) *Wohl's Reaction (1893).*—The oxime of an aldose is boiled with acetic anhydride, when the *polyacetyl derivative* of a *nitrile* (formed by dehydration of the $-CH{:}N(OH)$ group) is produced; when this is hydrolysed, prussic acid is eliminated, and simultaneously the acetyl groups are saponified:



$$P.CH(OH).CHO \xrightarrow{NH_2OH} P.CH(OH).CH{:}N(OH) \xrightarrow{Ac_2O} P.CH(O.CO.CH_3).CN \xrightarrow{H_2O} P.CHO + HCN + CH_3.COOH.$$

(*b*) *Ruff's Reaction* (1898).—By gentle oxidation an aldose is converted to the corresponding monobasic acid; for example, *glucose* (I) yields *gluconic acid* (II). By further oxidation, either with bromine in presence of lead carbonate, or with hydrogen dioxide in presence of basic iron acetate, this acid evolves carbon dioxide and water, and becomes *arabinose* (III), the corresponding sugar in the next lower monosaccharide series:



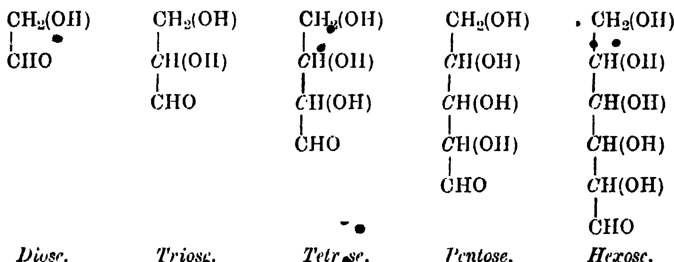
$$\underset{(I)}{P.CH(OH).CHO} \rightarrow \underset{(II)}{P.CH(OH).COOH} \rightarrow \underset{(III)}{P.CHO} + CO_2 + H_2O.$$

CHAPTER XIII

THE CARBOHYDRATES: CONFIGURATIONS OF THE MONOSACCHARIDES

I. THE POSSIBLE ISOMERS OF THE VARIOUS ALDOSES

WHEN we examine the constitutional formulæ of the aldo-dioses to aldo-hexoses (inclusive), we find that asymmetric carbon atoms exist in all of them except the dioses. The formulæ are as follows:—



Diose. *Triose.* *Tetrose.* *Pentose.* *Hexose.*

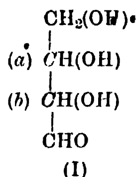
Hence there is only one possible *diose* (according to the accepted theories), and in point of fact, *glycollic aldehyde*, which is the only diose known, is only found to exist in one form.

The formula for a *triose*, however, possesses one asymmetric carbon atom, so that there are two possible active forms of this compound (*dextro-* and *lævo-*), and, of course, a third (*racemic*) modification resulting from the presence of each optical isomeride in equal amounts in a mixture of the two.

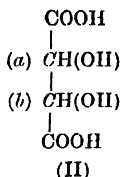
With the higher monosaccharides complications ensue, owing to the presence of more than one asymmetric carbon atom. Employing the *tetroses* (I) by way of example, it is seen that

either asymmetric carbon atom (*a*) or (*b*) may be *dextro-* or *lævo-*rotatory, so that we have the following combinations :—

(*a*) dextro- + (*b*) dextro- ; (*a*) dextro- + (*b*) lævo- ;
(*a*) lævo- + (*b*) dextro- ; (*a*) lævo- + (*b*) lævo-.



(I)



(II)

It must be explained here that, if the last group at each end of the molecule is the same, as in tartaric acid (II), the number of active forms is less, for in such a case the contributions of the asymmetric carbon atoms next to these groups to the molecular asymmetry are exactly equal.

Consequently the forms (*a*) dextro- + (*b*) lævo- and (*a*) lævo- + (*b*) dextro- are identical, and are represented by the inactive *meso-* form produced by this "internal compensation."

This fact is important in connection with the configuration of the polyhydric alcohols and dibasic oxy-acids closely related to the monosaccharides.

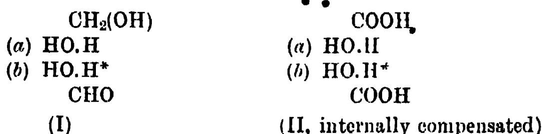
Proceeding to the *pentoses*, it will be found by similar procedure to the above that eight active forms (four *dextro-* and four *lævo-*) are here possible. A less cumbersome method of determining the number of possible isomers of the various sugars is due to van't Hoff, who showed that if n asymmetric atoms are present in the molecule, the total number of active forms will be 2^n.

Hence the number of optical isomerides in the different classes is as follows :—

Monosaccharides.	*No. of asymmetric atoms.*	*No. of isomerides.*
Dioses.	0	$2^0 = 1$
Trioses.	1	$2^1 = 2$
Tetroses.	2	$2^2 = 4$
Pentoses.	3	$2^3 = 8$
Hexoses.	4	$2^4 = 16$
Heptoses.	5	$2^5 = 32$

We will next enumerate in a series of tables the different configurations corresponding to the *tri-*, *tetra-*, *pent-*, and *hex-oses*, and their correlated *polyhydric alcohols* and *dibasic oxy-acids*.

This will be facilitated by the use of a very general conventional formulation, in which the asymmetric carbon atoms are represented by dots, an atom asymmetric in one sense (with respect to the adjacent groups) by writing the H atom to the right of the OH group, and one in the other sense by the H atom being to the left of the OH group. Thus the above formulæ for the forms (*a*) *dextro-* (*b*) *lævo-* of a tetrose (I) and tartaric acid (II) become:



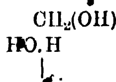
(I)	(II, internally compensated)
$CH_2(OH)$	COOH
(*a*) HO.H	(*a*) HO.H
(*b*) HO.H*	(*b*) HO.H*
CHO	COOH

In this way the different configurations of each series resolve themselves into a number of enantiomorphously-related pairs, to which the *d-* and *l-* forms of the actual different sugars correspond. It is, of course, impossible to say that, of any pairs of configurations, one corresponds to the *d-*, and the other to the *l-*, sugar; but it is merely necessary arbitrarily to assign one formulation to represent one form of the actual sugars, and conversely.

In the ensuing tables, the arbitrary "*dextro-*" forms are given in the first, and the corresponding "*lævo-*" in the second columns.

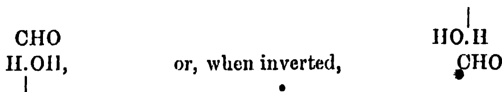
* At first sight it seems that the asymmetric atom (*b*) has also been written as a *dextro-* component, but it must be always borne in mind that the space-formulæ in this chapter are given only in the form of projections on a plane surface (the leaf of the book); hence care must be exercised as to the point of view from which the atoms are regarded.

The simplest method of ensuring accuracy is mentally to consider each individual group in corresponding positions; in this way we may write (in the above formula), a *dextro-* atom attached to the (CH_2OH) residue as:



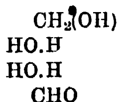
$CH_2(OH)$
HO.H
|

The *lævo-* form of the remaining part of the molecule is therefore



CHO
H.OH, or, when inverted, HO.H
| CHO

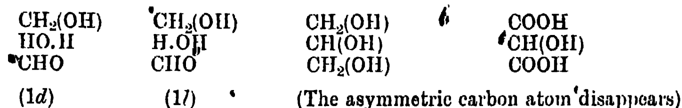
Thus the form (*a*) *dextro-* + (*b*) *lævo-* is:



$CH_2(OH)$
HO.H
HO.H
CHO

The Trioses

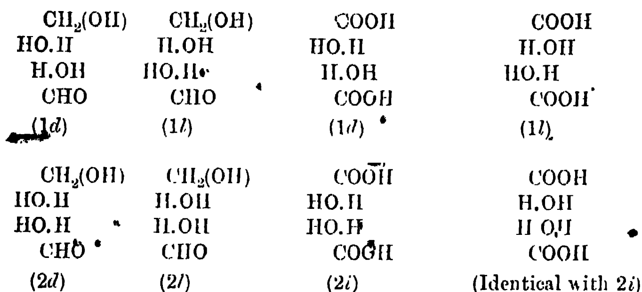
Possible active isomers : 2. *Corresponding active alcohols or dibasic acids :* 0.



(1*d*) (1*l*) (The asymmetric carbon atom disappears)

The Tetroses

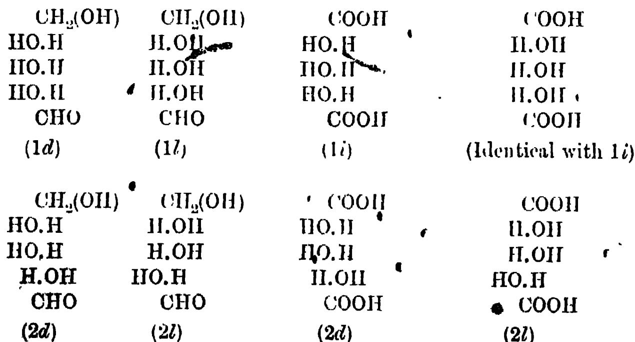
Possible active forms : 4. *Corresponding active alcohols or dibasic acids :* 3.



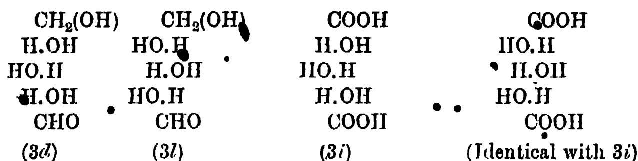
These formulæ represent respectively the *d*-, *l*-, and *i*-(*meso*-) forms of tartaric acid.

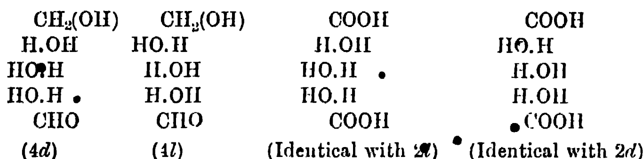
The Pentoses

Possible active forms : 8. *Corresponding active alcohols or dibasic acids :* 4.



THE PENTOSES—*Continued*



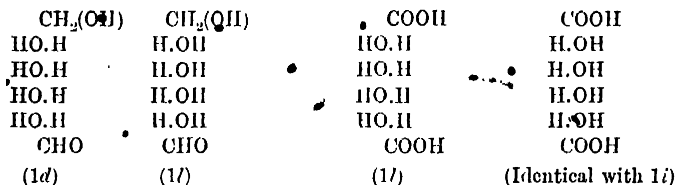


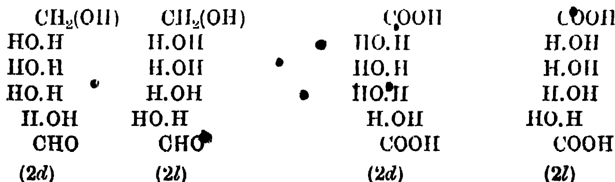
There are thus only *four* distinct forms of the trioxyglutaric acids. In these acids the central carbon atom has lost its asymmetric nature (being united to two $-CH(OH).COOH$ radicles), whilst of the remaining two, in acids 1*i* and 3*i*, one is *dextro-* and the other *lævo-*, the asymmetry of each being the same. Hence *meso*-acids result.

The acids from sugars 4*d* and 4*l* are respectively the same as those from 2*l* and 2*d*.

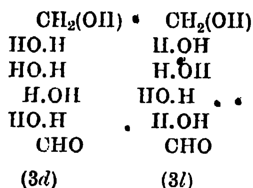
THE HEXOSES

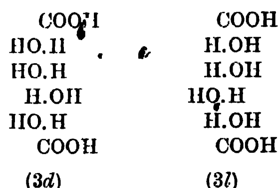
Possible active forms: 16. *Corresponding active alcohols or dibasic acids*: 10.

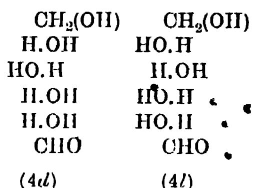


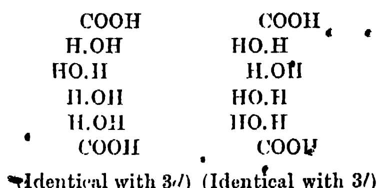


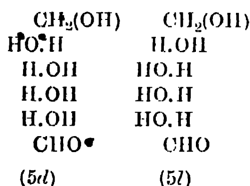
THE HEXOSES—*continued*

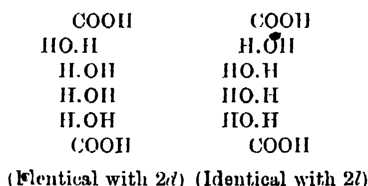

(3*d*) (3*l*)

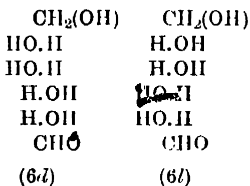

(3*d*) (3*l*)

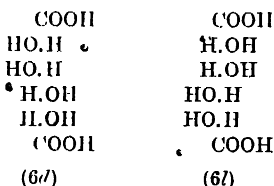

(4*d*) (4*l*)

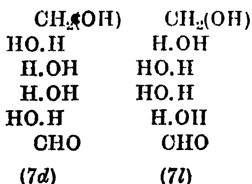

(Identical with 3*l*) (Identical with 3*l*)

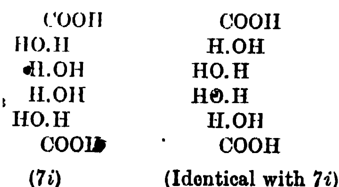

(5*d*) (5*l*)


(Identical with 2*d*) (Identical with 2*l*)


(6*d*) (6*l*)


(6*d*) (6*l*)


(7*d*) (7*l*)


(7*i*) (Identical with 7*i*)

THE HEXOSES—*continued*

$CH_2(OH)$	$CH_2(OH)$	COOH	COOH
H.OH	HO.H	H.OH	HO.H
HO.H	H.OH	HO.H	H.OH
H.OH	HO.H	H.OH	HO.H
HO.H	H.OH	HO.H	H.OH
CHO	CHO	COOH	COOH
(8*d*)	(8*l*)	(8*d*)	(8*l*)

Hence, there should be *ten* tetraoxyadipic acids—two *meso-*, four *dextro-*, and four *lævo-* forms.

The number of active forms of the sugars thus demanded by stereo-chemical theory is known to be satisfied by the facts as regards the trioses (2), tetroses (4), and pentoses (8), the numbers in brackets indicating the members actually discovered up to the present in each series.

Again, only two or three of the possible aldohexoses remain to be accounted for, but in the higher classes very few members are yet known. It is thus unnecessary to enter into details of the configurations of the heptoses, octoses, or nonoses.

It should be distinctly understood that, in addition to the choice of the above enantiomorphous formulæ being purely arbitrary, it happens not infrequently that by chemical means a substance such as *d*-glucose is converted into a closely-related derivative whose optical rotatory power is of quite opposite sign; and that, in such cases, in order to preserve the above system, the derivative so produced would still be referred to as a *dextro*-compound, in spite of its actual *lævo*-rotation.

We shall now describe how, in the more important cases, the determination of the configuration of particular sugars has been achieved. This problem can be attacked from several points, one of the simplest being to commence with the consideration of the individual pentoses.

II. Configuration-Determination of the Aldopentoses

As shown on p. 232, there are eight possibilities to be considered; these arrange themselves in four pairs of optical enantiomorphs, so that we need only consider the *four dextro-* (or the four *lævo-*) forms—for example, those corresponding to configurations 1*d*, 2*d*, 3*d*, and 4*d*.

Eight aldopentoses are already known, namely, *d*- and *l*-arabinose, *d*- and *l*-ribose, *d*- and *l*-xylose, and *d*- and *l*-lyxose.

The problem is very easily solved in this case:—

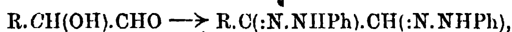
(i) Of these sugars, *arabinose* and *ribose* give the same osazone.

(ii) On oxidation, *arabinose* gives an optically active dibasic acid; *ribose* gives an optically inactive dibasic acid; *xylose* gives an optically inactive dibasic acid.

(iii) When submitted to Kiliani's reaction (p. 227), and subsequently oxidized to a dibasic acid, *arabinose* gives a mixture of two acids, both optically active; *lyxose* gives a mixture of two acids, one active and one inactive.

Let us consider what these reactions imply.

(i) It is known that an osazone is formed by the oxidation of a – *C*H(OH) – group adjacent to the carbonyl radicle. Thus



R.*C*H(OH).CHO ⟶ R.C(:N.NHPh).CH(:N.NHPh),

so that the asymmetry of the carbon atom next to the group – CHO is destroyed.

If, then, two sugars give the same osazone, their configurations must be identical, except as regards the carbon atom next to the – CHO group.

Hence, *arabinose and ribose must be either* (1 *and* 2) *or* (3 *and* 4).

(ii) Pentoses 1 and 3 give optically inactive dibasic acids.
Pentoses 2 and 4 give optically active dibasic acids.

Hence, *arabinose is either* 2 *or* 4, *ribose and xylose are* (1 *and* 3).

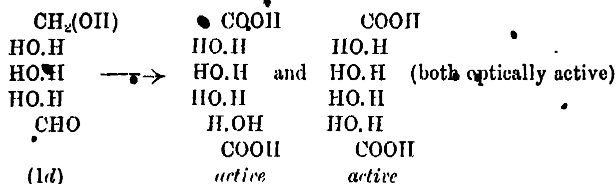
So that *lyxose must be either* 4 *or* 2.

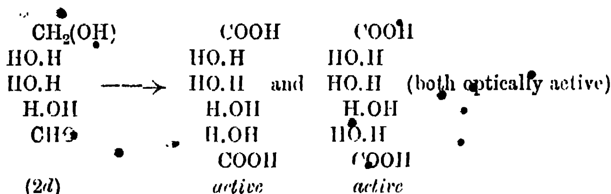
(iii) By Kiliani's reaction, a new asymmetric carbon atom is formed in the molecule:—

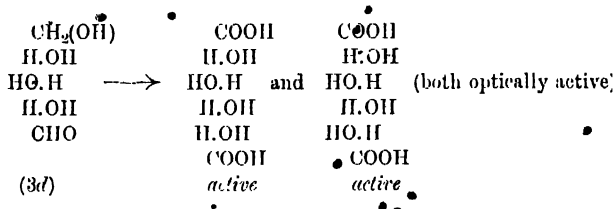


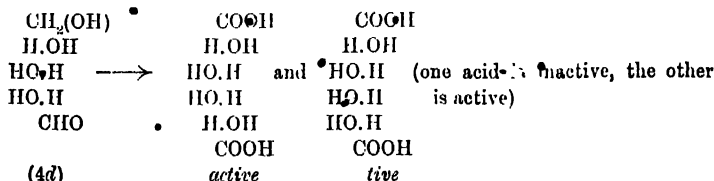
R.CHO ⟶ R.*C*H(OH).CN ⟶ R.*C*H(OH).COOH.

Applying this, after oxidation of the new sugar to a dibasic acid, to the pentoses 1 *d*- 4*d*, we have :—









Now, from (ii),

arabinose and *lyxose* form (2 and 4).

But *lyxose* gives an inactive and an active acid by Kiliani's reaction.

Therefore *lyxose* must be 4.

So that *arabinose* is 2.

Hence, by (i),

since *arabinose* and *ribose* are (1 and 2) or (3 and 4)
arabinose being 2, *ribose* corresponds to 1.

Thus finally,

d- and *l-Ribose* correspond to configurations				1*d* and 1*l*
d- and *l-Arabinose*	,,	,,	,,	2*d* and 2*l*
d- and *l-Lyxose*	,,	,,	,,	4*d* and 4*l*

and so, by elimination,

d- and *l-Xylose*	,,	,,	,,	3*d* and 3*l*

III. Configuration-Determination of Glucose, Mannose, and Galactose (Aldohexoses)

(a) *Glucose and Mannose.*

The configuration of glucose can be determined, from due consideration of the various chemical relationships between the hexoses, on lines similar to those developed for the pentoses; but it is very much more simple to determine in the first place the configuration of the latter class, and thus, knowing that of arabinose, to use this in discovering that of glucose.

We need then quote only two reactions of glucose and mannose in order definitely to assign the appropriate stereochemical structure to each :—

(i) By Kiliani's reaction, *l*-arabinose yields a mixture of two hexoses, *l-glucose* and *l-mannose*.

(ii) The dibasic acid formed when glucose is oxidized, *saccharic acid*, is also produced when another hexose, *gulose*, is similarly treated.

The following deductions therefore ensue :—

(i) Since the *dextro*- and *lævo*- forms of a compound are identical except in the sign of their rotation, we may make the (*non-essential*, but for the present purpose simplifying) assumption that *d*-arabinose, will give the *dextro*-hexoses of which the *lævo*-compounds from *l*-arabinose are the optical antipodes.

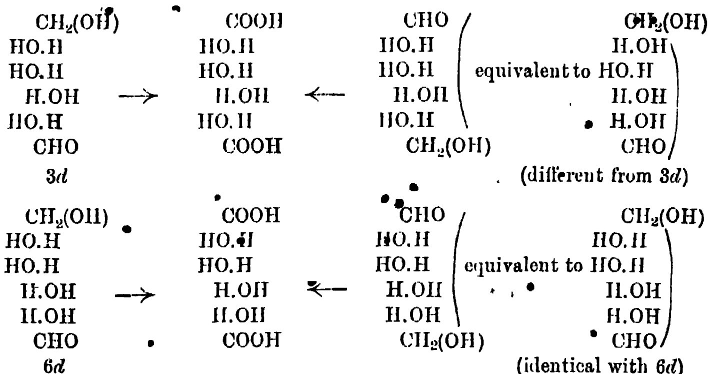
As shown above, *d*-arabinose is pentose 2*d*, so that the hexoses formed from it by Kiliani's reaction will be represented thus:

d-Arabinose	*d-Glucose*	*d-Mannose*
$CH_2(OH)$	$CH_2(OH)$	$CH_2(OH)$
HO.H	HO.H	HO.H
HO.H	HO.H	HO.H
H.OH	H.OH	H.OH
CHO	HO.H	H.OH
	CHO	CHO
2*d* (Pentose)	3*d* (Hexose)	6*d* (Hexose)

These sugars correspond with configurations 3*d* and 6*d* in the table of possible active aldohexoses (pp. 233-35).

(ii) When two different sugars give the optically identical dibasic acid by oxidation, it is plainly implied that the configurations of each of the four asymmetric carbon atoms are the same in each molecule (for otherwise an optically different acid will be produced in one case to that formed in the other). Hence the only distinction in the sugars can be that their primary alcohol, (CH_2OH-) and aldehydic ($-CHO$) groups are, so to speak, interchanged.

Let us see, then, what ha s when we interchange these groups in hexoses 3*d* and 6*d*:



In other words, the dibasic acid from 6*d* can only result from this one sugar, whereas that from 3*d* can be formed by the oxidation of either of two sugars.

Now, *saccharic acid* can be produced by the oxidation of either *glucose* or *gulose*, so that, since glucose is either 3*d* or 6*d*, it must be 3*d*.

Hence, *d*- and *l-Glucose* correspond to configurations 3*d* and 3*l*,
and therefore, *d*- and *l-Mannose* ,, ,, ,, 6*d* and 6*l*.

In confirmation of this view, and more particularly of the evidence afforded by Kiliani's reaction when a new asymmetric carbon atom was introduced, we find that *glucose* and *mannose* yield the same osazone (*i.e.* their configurations are identical except as regards that of the carbon atom next to the aldehydic group).

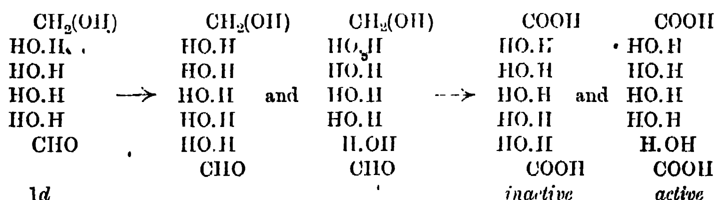
(*b*) *Galactose.*

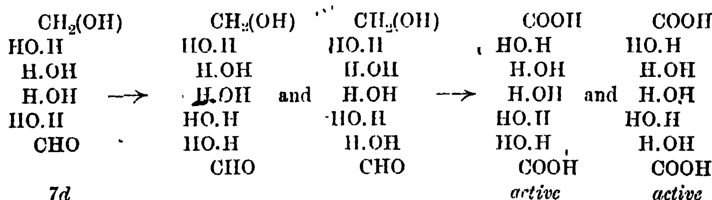
(i) On oxidation to a dibasic acid, *galactose* yields an optically inactive product.

(ii) By Kiliani's reaction, and subsequent oxidation, two optically active acids are produced.

Hence, (i) from the table of hexoses, we see that the only sugars giving inactive acids are 1*d* (1*l*) and 7*d* (7*l*).

We have now to investigate the acids formed from sugars 1*d* and 7*d* by the oxidation of the product of Kiliani's reaction :—



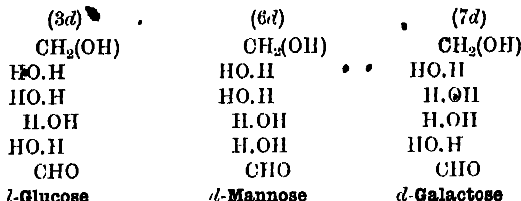


The first acid formulated from hexose 1*d* is a *meso*-compound, its central carbon atom having become non-asymmetric, whilst those on either side are respectively *lævo-* and *dextro-*.

Hence only 7*d* gives two active acids, and therefore *galactose* corresponds to this configuration.

Maintaining the convention as to *dextro-* and *lævo-* configura-

tions which was mentioned on page 231, we have, therefore, the following stereoformulæ for the three most important of the aldohexoses :—



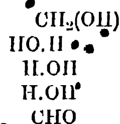
IV. Configuration-Determination of the Aldotetroses and the Tartaric Acids

(a) The tetroses.

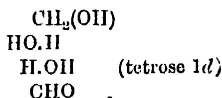
The table of aldotetroses on p. 232 shows that only two pairs of enantiomorphous sugars have to be discussed, namely, *d*- and *l-erythrose*, and *d*- and *l-threose*.

Now, it has been found that *l-xylose* (pentose 3*l*), by "degradation" to a tetrose according to Wohl's reaction (page 228) furnishes *l-threose*.

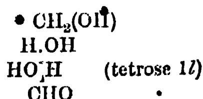
Therefore, since *l-xylose* is represented by :—



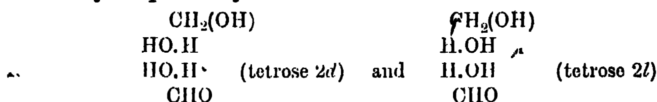
l-threose must correspond to :—



so that *d-threose* is :—



Correspondingly, *d-* and *l-erythrose* are represented stereochemically respectively as :—

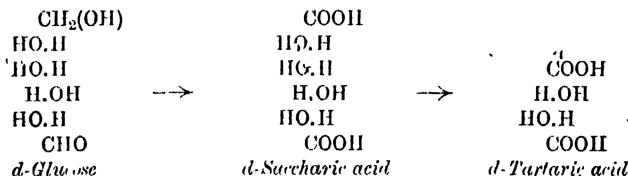


(*b*) *The tartaric acids and malic acids.*

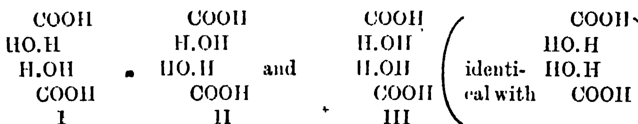
The configurations of the various tartaric acids and malic acids can also be derived in accordance with the notation employed for the sugars.

Thus, *l-threose* when oxidized to a dibasic acid by the customary means is found to give *l-tartaric acid*, which therefore corresponds to configuration I below.

On the other hand, *d tartaric acid* is produced when *d-saccharic acid* (from *d-glucose*) is further oxidized, and possesses the configuration II below :—

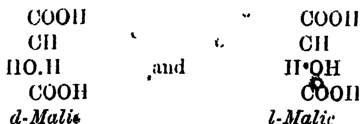


The configurations of *l-*, *d-*, and *i-* (*meso-*) *tartaric acids* are thus respectively :—



with respect to the configuration of *d-glucose* assigned as above.

Finally, since *d-* and *l-tartaric acids* are respectively reduced to *d-* and *l-malic acids* by the action of hydriodic acid, the optically active malic acids will be represented by :—



V. Configuration-Determination of Fructose and Sorbinose (Ketohexoses)

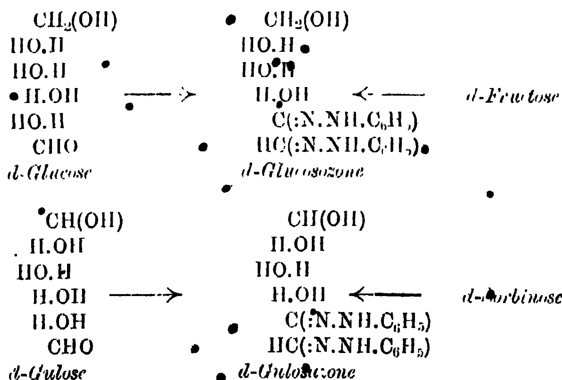
It is very easy to assign the appropriate configurations to the ketohexoses which contain the carbonyl group adjacent to the terminal alcoholic residue: *—


$CH_2(OH).CH(OH).CH(OH).CH(OH).CO.CH_2(OH).$

As already mentioned (p. 226), it is known that fructose (and also sorbinose) belong to this type of compound. Furthermore, the ketoses possess one asymmetric carbon atom less than the corresponding aldoses.

Now, in the formation of *osazones* from aldohexoses, the asymmetry of the carbon atom adjacent to the aldehyde group is destroyed (compare p. 236); and again *d-"fructosazone"* is identical with *d-glucosazone*, whilst the *osazone* of *d-gulose* (which, as we found on p. 239, corresponds to *d-glucose* with the positions of the $CH_2(OH)$ - and -CHO groups interchanged) is identical with that obtained when *d-sorbinose* is treated with excess of phenylhydrazine.

These relations determine the configuration of both ketoses :—



* As a matter of fact, ketoses with the -CO- group in other positions with respect to the $-CH_2(OH)$ radicle are not known with certainty.

The configurations of *d*- and *l*-*Fructose* and of *d*- and *l*-*Sorbinose* are consequently as follows :—

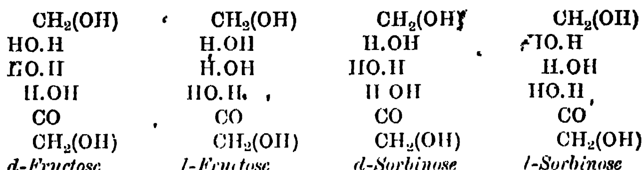
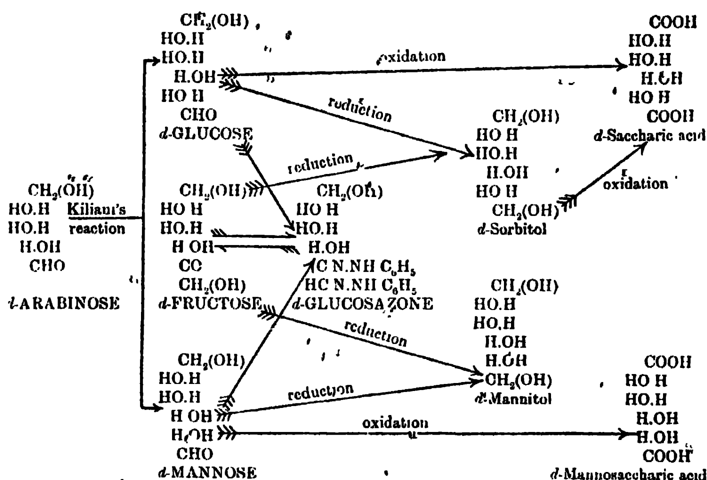


DIAGRAM OF THE CHIEF RELATIONS BETWEEN *d*-GLUCOSE, *d*-FRUCTOSE, AND *d*-MANNOSE



CHAPTER XIV

THE CARBOHYDRATES: MONOSACCHARIDES AND CYCLIC SUGARS AND THEIR DERIVATIVES

I. The Dioses

FROM the point of view of our original definition of a monosaccharide as a compound of the formula $C_m H_{2m} O_m$, it is obvious that the first term of the series will be *formaldehyde*, CH_2O; we have, indeed, included it in the classification of carbohydrates given in the course of chapter xii. (p. 219).

Bearing in mind, however, the further characteristics of these substances which have been developed in the two preceding chapters, it will be seen that other conditions besides the possession of an empirical formula $[CH_2O]_m$ must be fulfilled by a monosaccharide :—

(i) It must possess a carbonyl group, either aldehydic or ketonic, and also one or more alcoholic groups.

(ii) To every carbon atom in the molecule other than that of the carbonyl residue, must be attached a hydroxyl group.

These restrictions exclude formaldehyde from consideration as a " saccharide," and leave as first member of the series the *monoaldehyde* of *glycol*, $C_2H_4O_2$ or CH_2 (OH)CHO.

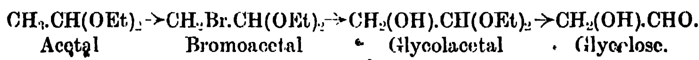
This division is not entirely mechanical, for there exist well-marked physical distinctions between formaldehyde and the monosaccharides. The latter substances are syrupy, viscous liquids or crystalline solids, with very sweet taste, but no smell; formaldehyde, CH_2O, is a gas, with a pungent, choking smell and acrid taste.

It is true that the polymeric forms of formaldehyde are both liquid and solid, but these substances (which possess the formula

$(CH_2O)_n$, *n* being greater than 1) are more closely connected with the higher monosaccharides than with formaldehyde itself, and indeed, it is possible to polymerise formaldehyde into compounds of the formula $(CH_2O)_6$, which have been found to belong to the hexoses.

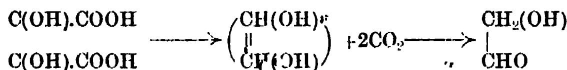
We will return to this point in the next chapter (p. 286) when dealing with the synthetic production of the hexoses, and now proceed briefly to describe the simplest class of true monosaccharides, the *dioses*, $C_2H_4O_2$, which includes only the compound already mentioned, *glycollic aldehyde*.

Glycollic aldehyde or *glycolose* $CH_2(OH).CHO$, was obtained originally in aqueous solution by the careful treatment of monobromacetaldehyde, $CH_2Br.CHO$, with baryta water, or from its acetal (from bromoacetal and silver oxide) when this compound was treated with aqueous hydrochloric acid :—



$$\underset{\text{Acetal}}{CH_3.CH(OEt)_2} \rightarrow \underset{\text{Bromoacetal}}{CH_2Br.CH(OEt)_2} \rightarrow \underset{\text{Glycolacetal}}{CH_2(OH).CH(OEt)_2} \rightarrow \underset{\text{Glycolose.}}{CH_2(OH).CHO.}$$

It was first prepared pure by Fenton in 1894 by the action of warm water on *dioxymaleic acid* (p. 274) :—



$$\begin{matrix} C(OH).COOH \\ C(OH).COOH \end{matrix} \longrightarrow \left(\begin{matrix} CH(OH) \\ \| \\ CH(OH) \end{matrix}\right) + 2CO_2 \longrightarrow \begin{matrix} CH_2(OH) \\ | \\ CHO \end{matrix}$$

Glycolose separates from its concentrated aqueous solution after prolonged standing in a vacuum in the form of large colourless crystals which melt at 95°. Like the higher sugars, it is readily soluble in water, less so in cold alcohol, and only sparingly in ether. It readily reduces Fehling's solution, being thereby transformed to glyoxylic, and eventually to oxalic acid. It responds to the various qualitative colour, *etc.*, tests for the sugars (*cf.* p. 223), and with phenylhydrazine yields an *osazone*, $CH(:N.NH.C_6H_5).CH(:N.NH.C_6H_5)$, which, as would be expected, is identical with the diphenylhydrazone of *glyoxal*, $CHO.CHO$, and melts at 177°.

On the other hand, *glycolose* resembles formaldehyde in its condensations to members of the tetrose and hexose series in presence of dilute alkalies.

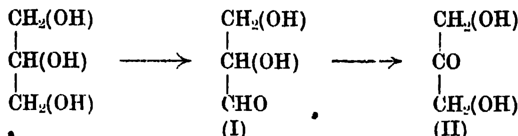
By addition of ammonium cyanide to *glycolose*, and subsequent careful saponification, *serin* (chap. xi. p. 208) is produced :—



$$CH_2(OH).CHO \rightarrow CH_2(OH).CH(NH_2).CN \rightarrow CH_2(OH).CH(NH_2).COOH.$$

II. The Trioses

When glycerol is treated with bromine water or hydrogen dioxide, a mixture of two primary oxidation products results, and this is known as *crude glycerose.* Its constituents are *glyceric aldehyde* or *glycerose* (I) and *dioxyacetone* (II).



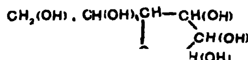
This mixture is a syrupy liquid, which possesses the characteristic taste and reducing reactions of a sugar, and which, when treated with cold dilute alkali, passes into a bimolecular condensation product, $C_6H_{12}O_6$, which is a mixture of various hexoses (see chap. xv, p. 287).

The separation of the constituents of crude glycerose has not yet been effected, but each has been prepared in a pure condition within the last few years by synthetic processes.

A. Aldotrioses. *Glycerose* was first obtained pure by Wohl in 1898; by means of a complicated process he prepared it from acrolein, CH_2:CH.CHO. More recently it has been produced in very good yield by warming dibromacrolein with water.



It is a crystalline solid melting at 137°, and in aqueous solution exists both in bi- and in mono-molecular forms. The bimolecular modification has been supposed to be lactide-like (p. 167) or a kind of lactone,



Glycerose is the lowest sugar which contains an asymmetric carbon atom, but its optically active forms are not yet known in the pure state.

I. *Glycerose* has resulted, together with other fermentation products, from the bacterial action of certain specific organisms on higher saccharides such as starch or cane-sugar.

B. Ketotrioses. *Dioxyacetone* has been obtained pure by several methods :—

(i) Biochemically, by the action of *Bacterium xylinum* on dilute aqueous glycerol.

(ii) Biochemically, by the action of *Bacterium roseus* on glucose.

(iii) Chemically, from dibromacetone and alkali :—



$$CH_2Br.CO.CH_2Br \longrightarrow CH_2(OH).CO.CH_2(OH).$$

(iv) Chemically, from glycerol in presence of ozonized oxygen (Harries).

(v) Chemically, from glycerine by oxidation with quinone in sunlight (Ciamician and Silber).

Dioxyacetone exists in both crystalline and amorphous states, and very readily polymerises to hexoses, etc.

C. Methyltrioses. Several homologues of glycerose are known, such as methylglycerose and trimethylglycerose.

Methylglycerose, $CH_3.CH(OH).CH(OH).CHO$, was obtained by Wohl in 1902 from crotonic aldehyde, $CH_3.CH{:}CH.CHO$, in the same manner as that by which acrolein was converted to glycerose.

Trimethylglycerose, $(CH_3)_2.C(OH).CH(OH).CO.CH_3$, was prepared by Harries by careful oxidation of mesityl oxide, $(CH_3)_2.C{:}CH.CO.CH_3$, with ice-cold permanganate.

III. The Tetroses

In the same way that glycerol gives crude glycerose (glyceric aldehyde and dioxyacetone) when oxidized, the normal tetrahydric alcohol *erythritol* (see p. 267) yields a mixture of aldo- and keto-tetroses on oxidation with hydrogen dioxide, sodium hypobromite, or quinone (in presence of sunlight); and it has not yet been found practicable to separate the components of the somewhat complex mixture of tetroses formed. Three of the aldotetroses have, however, been prepared from the corresponding pentoses by Wohl's or Ruff's degradation reactions (p. 228).

Aldotetroses. ***d-Erythrose, l-erythrose,*** **and** ***l-threose*** **have been obtained by the above-mentioned processes respectively from** ***d*****-arabinose,** ***l*****-arabinose, and** ***l*****-xylose. All three sugars are syrups which show the general physical and chemical characteristics of the class, and these, together with the configuration of each (as given on p. 232) may be given in tabular form :—**

	Ref. on p. 232.	Confign.	M.p. of osazone	Reduction product.	Oxidation product. (dibasic acid).
d-Erythrose	2d	HO.H HO.H	166°	i-Erythritol.	i-Tartaric acid.
l-Erythrose	2l	H.OH H.OH	164°	i-Erythritol.	i-Tartaric acid.
d-Threose	1d	HO.H H.OH	191°	l-Erythritol.	l-Tartaric acid.

d-Erythrose is *lævo*-rotatory, whilst *l*-erythrose and *l*-threose are *dextro*-rotatory; this is a natural consequence of the notation used, which (as already pointed out on p. 235) has reference to the genetic configurational relationships running through the whole of the monosaccharide series, and not to the necessary sign of the actual rotatory power of any one sugar.

Racemic (*d*- + *l*-) erythrose cannot be prepared by degradation of racemic arabinose, for on crystallization of the product one or other active form always separates out first (just as racemic tartrates can in general only be obtained within certain limits of temperature). It has, however, been prepared by mixing equal quantities of the *dextro*- and *lævo*-sugars, and gives an optically inactive *osazone*, melting at 161°, (*d*- + *l*-) erythritol (by reduction), m.p. 72° (*cf.* p. 268), and (*d*- + *l*-)tartaric acid (on oxidation).

Keto- and Methyl-Tetroses are known, but are not of sufficient interest to warrant a detailed description here.

IV. The Pentoses

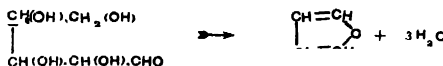
So far as is at present known, the dioses, trioses, and tetroses do not occur naturally, and have only been obtained in the laboratory; some of the pentoses, on the other hand, are found fairly plentifully in nature, a fact which conduces to the interest of their study.

In addition to all the usual reactions of the monosaccharides, they are distinguished by two peculiarities :—

(i) They are not fermentable by the enzymes present in yeast (in contrast to most of the hexoses).

(ii) They condense extremely readily to furfurane derivatives

(by distillation with dilute mineral acid). So complete is this change that it is commonly utilized for the quantitative determination of pentoses, and also as a qualitative test by means of the colour reaction given by furfuraldehyde with certain polyhydric phenols such as orcinol or phloroglucinol (p. 223) :—



Reduction of the pentoses furnishes the corresponding pentahydric alcohols, some of which also occur in plants; oxidation leads firstly to *n*-tetraoxyvaleric acids, and then to *n*-trioxyglutaric acids.

The *ketopentoses* are not very definitely known, but we must consider some of the more important *aldo-* and *methyl-pentoses*.

A. ALDOPENTOSES.

(i) *Arabinose.* This is known in all three forms, *dextro-*, *lævo-* and *racemic*. *d-Arabinose* has not yet been found in nature, but was prepared from *d*-glucose by Wohl in 1893. *l-Arabinose*, however, is found in the form of glucosides or of pentacelluloses (p. 312) in certain gums (notably in cherry gum and gum arabic as arabinic acid, $C_{12}H_{22}O_{11}$) and also in carnivorous urine. (*d-* + *l-*) *Arabinose* occurs in urine in certain diseases and is prepared chemically by crystallizing equal amounts of the active forms together from alcohol.

Reduction of the arabinoses gives the *arabitols*, and oxidation, the monobasic *arabonic*, and the dibasic *trioxyglutaric acids.*

(ii) *Xylose* is also known in its three optical modifications, of which the *lævo*-antipode occurs in various vegetable and animal nucleo-proteids (*e.g.*, in pepsin, urine, and beechwood gum). *d-* and (*d-* + *l-*) *Xyloses* have only been artificially prepared, the former by oxidation of *d*-gulonic lactone (Ruff's reaction, from *d*-gulose, p. 239), the latter from equal quantities of the active forms.

The xyloses are transformed to *xylitols*, stereoisomeric with the arabitols, by reduction; oxidation leads to *xylonic* (monobasic) and to *trioxyglutaric* (dibasic) acids.

(iii) *Lyxose* is only known in its *dextro*-form, prepared from *d*-galactose by either Wohl's or Ruff's reactions.

Its reductions produces *d-arabitol.*

(iv) *l-Ribose* has been obtained from *l*-ribonic acid, the corresponding monobasic acid, which results by intramolecular rearrangement when *l*-arabonic acid is heated with quinoline.

By warming with alkalies it is transformed into an equilibrium mixture of *l*-arabinose and *l*-ribose (*l*-arabinose of course behaves similarly).

Racemic ribose has been prepared in analogous fashion by warming (*d*- + *l*-) arabinose with dilute aqueous alkali.

Reduction of *l*-ribose gives *i*-(*meso*-)*adonitol*, an alcohol which occurs in the plant *Adonis vernalis* or Pheasant's Eye (p. 269).

The signs of the *actual* optical activity of these various sugars are as follows :—

d-Arabinose	—	*l*-Arabinose	+
d-Xylose	—	*l*-Xylose	+
d-Lyxose	—		—
	—	*l*-Ribose	+

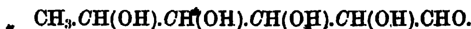
B. Methylpentoses.

Rhamnose (also known as *isodulcite*) is a methyl homologue of the pentoses found in many glucosides, very frequently in combination with the flavone dyes (chap. vi. p. 90). Thus it is combined with quercetin in *quercitrin*, $C_{21}H_{22}O_{12}$, with fisetin in *fisetin-glucoside*, $C_{36}H_{30}O_{16}$, with *d*-glucose and hesperetin in *hesperidin*, $C_{50}H_{60}O_{29}$, etc. etc.

It is a dextrorotatory sugar, existing in the hydrated ($+H_2O$) as well as in the anhydrous state, whilst in the latter condition there is reason to believe that at least three isomeric or tautomeric modifications may exist.

On reduction it passes into *rhamnitol* (p. 269), whilst the monobasic acid formed from it by oxidation is known as *rhamnonic acid* ; further oxidation produces (dibasic) *l-trioxyglutaric* (so that here the methyl group has disappeared).

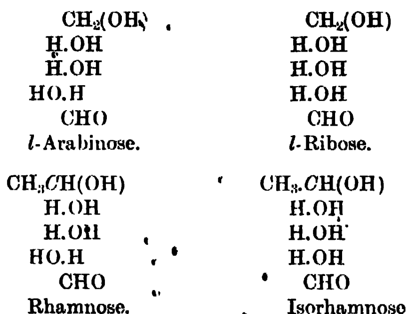
Distillation with dilute sulphuric acid produces *α*-methylfurfuraldehyde, so that, since rhamnose is an aldose, its formula must be



$CH_3.CH(OH).CH(OH).CH(OH).CH(OH).CHO.$

When *rhamnonic acid* is heated with quinoline, *isorhamnonic acid* is formed, and reduction of the lactone of this acid gives an isomeric methylpentose known as *isorhamnose.*

Isorhamnose and *rhamnose* yield the same *ozasone* with phenylhydrazine. Since the *l-trioxyglutaric acid* from rhamnose is identical with that obtained when *l*-arabinose is oxidized (p. 250), and since, as shown above, *l*-arabonic acid yields *l*-ribonic acid with quinoline, it is very likely that *rhamnose* is a *methyl-l-arabinose*, and *isorhamnose* a *methyl-l-ribose* :—



The following table summarizes the chief properties of the above pentoses :—

	Ref. on p. 232.	*M.p.*	*M.p. of osazone.*	*Redn. product.*	*1st Oxidn. product.*		*2nd Oxidn. product.*	
-Ribose	1*l*	Syrup	160°	*i*-Adonitol	*l*-Ribonic	acid	*i*-Trioxyglutaric	acid
d-Arabinose	2*d*	158°	160°	*d*-Arabitol	*d*-Arabonic	,,	*d*- ,,	,,
l- ,,	2*l*	160°	160°	*l*- ,,	*l*- ,,	,,	*l*- ,,	,,
(*d*- + *l*-) Arabinose	—	164°	168°	(*d*- *l*-) ,,	(*d*-*l*-) ,,	,,	(*d*- *l*-) ,,	,,
d-Xylose	3*d*	143°	170°	*i*-Xylitol	*d*-Xylonic	,,	*i*- ,,	,,
l- ,,	3*l*	154°	170°	*i*- ,,	*l*- ,,	,,	*i*- ,,	,,
(*d*- + *l*-) Xylose	—	131°	210°	*i*- ,,	(*d*- *l*-) ,,	,,	*i*- ,,	,,
d-Lyxose	4*d*	101°	170°	*l*-Arabitol	*d*-Lyxonic	,,	*l*- ,,	,,
Rhamnose	?	105°	180°	Rhamnitol	Rhamnonic	,,	*l*- ,,	,,
Isorhamnose	?	Syrup	180°	?	Isorhamnonic	,,	*i*- ,,	,,

V. THE HEXOSES

Although more numerous as a class than the preceding monosaccharides the various space-isomerides in the hexose series are not so important for the configuration-determination processes as those of the lower series. Hence they will not be discussed so fully, except in the cases of those sugars which owe their interest to their extremely wide distribution in nature.

It is also unnecessary again to describe the characteristic behaviour of the hexoses, as this subject has already received due attention (chap. xii. pp. 224-228; chap. xiii. pp. 238-244).

A. ALDOHEXOSES.

Glucose is by far the most important aldohexose, owing to the fact of the abundant occurrence of its *dextro-* form in plants and animals.

d-Glucose (*dextrose, grape sugar*) is found in the free condition in many ripe fruits (*e.g.* grapes or apples) and in honey; it exists still more abundantly in combination in the following classes of substances:—

(i) *Di-* etc., *-saccharides*. It is allied with *d-fructose* in *cane-sugar*, with *d-galactose* in *lactose*, whilst *maltose* is formed from two molecules of *d*-glucose.

(ii) *Polysaccharides*. Most of the starches and celluloses contain *d*-glucose in the combined state, and yield this substance when hydrolyzed by dilute sulphuric acid.

(iii) *Glucosides* (see also p. 297). *d*-Glucose also occurs in union with a variety of organic compounds in the numerous glucosides found in plants. A few common instances are

Amygdalin (*d*-glucose, benzaldehyde, and prussic acid).
Indican (*d*-glucose and indoxyl; the indigo plant glucoside.)
Myronic acid (*d*-glucose, allyl mustard oil and potassium bisulphate).
Arbutin (*d*-glucose and hydroquinone).
Salicin (*d*-glucose and salicyl alcohol).

d-Glucose may be prepared in the laboratory by the action of a mixture of 90% alcohol and 10% fuming hydrochloric acid on as

much powdered cane-sugar as it will dissolve. On standing for a few days at the room temperature, crystals of *d*-glucose commence to separate.

On a commercial scale, it is made by heating starch with boiling dilute sulphuric acid for some hours; the resulting product is by no means pure *d*-glucose, but may be recrystallized from methyl or ethyl alcohol containing a few drops of strong hydrochloric acid.

Crude glucose may also be purified by means of its compounds with lime or baryta—which are of the type of metallic alcoholates $(R.O)_2Ca$, etc.

Prepared in the above manner, *d-glucose* crystallizes from water with one molecule of water of crystallization and the "*d-glucose hydrate*" so formed melts at 86°.

By crystallization from absolute alcohol *anhydrous d-glucose* is obtained, and this forms hard tablets, which melt at 146°.

d-Glucosazone, which is also produced when phenylhydrazine reacts with either *d-fructose* or *d-mannose*, melts at 210°, and is *lævo*-rotatory.

The oxidation of *d-glucose* leads firstly to *d-gluconic acid*, $CH_2(OH).[CH(OH)]_4.COOH$, and then to *d-saccharic acid*, $COOH.[CH(OH)]_4.COOH$. When the lactone of this latter acid is reduced carefully, an aldehyde-acid intermediate between gluconic and saccharic, and known as *d-glucuronic* acid, $CHO.[CH(OH)]_4.COOH$, is produced (see pp. 275, 278).

Reduction of *d-glucose* produces *d-sorbitol* (p. 270) and traces of other alcohols, whilst alkalies tend to transform it to *d-mannose* and *d-fructose*.

Like most sugars, *d-glucose* exercises a selective action to various ferments; some, such as *zymase* (in yeast) convert it to alcohol and carbon dioxide, others do not attack it.

When first dissolved in water, *d*-glucose possesses a specific rotatory power $[\alpha_D] = +104°$, but this soon commences to fall off, and after the lapse of a few hours, becomes constant at $[\alpha_D] = +52°$.

This phenomenon is known as *mutarotation*, and is much hastened by warming the solution. Mutarotation has also been

observed with many other sugars, but has been most carefully studied in the case of *d-glucose*, and we will take this opportunity to discuss it.

At one time it was supposed that the alteration in rotation was due to formation or decomposition of polymeric or of "associated" glucose molecules; Raoult, however, measured the molecular magnitude of glucose solutions of varying specific rotatory power, and found in all cases that the molecular weight agreed with the molecular formula $(CH_2O)_6$.

It was therefore necessary to suppose that *d*-glucose existed in a number of isomeric or tautomeric modifications.

Now, Tanret (1895) succeeded in preparing three distinct forms of *anhydrous d-glucose* as follows:—

(i) *α-d-Glucose.* This is the form usually obtained as *hydrate* by crystallization from water below 30°. From boiling alcohol, as stated already, it separates anhydrous, melts at 140°, and has $[\alpha_D] = +106°$.

(ii) *β-d-Glucose.* This was prepared by evaporating an aqueous solution of *α-d*-glucose nearly to dryness on a water-bath, with constant stirring, when microscopic crystals separated, which possessed $[\alpha_D] = +52.5°$.

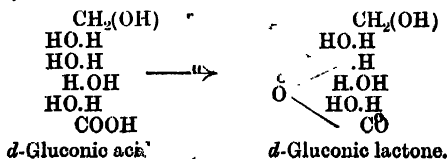
β-d-Glucose slowly forms a certain amount of *α-d*-glucose when mixed with water, or with alcohol, an *equilibrium mixture of the α- and β-d- forms* being produced.

(iii) *γ-d-Glucose.* The third form of *d*-glucose was obtained by heating the *α*-form to 105-110° (whereas the *β*-form results if the temperature is below 100°).

The production of the *γ-d-glucose* is not complete for some hours, but finally a product possessing $[\alpha_D] = +22.5°$ is produced, which in contact with water gradually passes into the *β*-variety, $[\alpha_D] = +52.5°$.

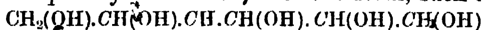
We have therefore to account for at least three isomeric forms of *d*-glucose.

Now the acid obtained from *d*-glucose by oxidation, *d-gluconic acid*, and also most of the known polyoxycarboxylic acids of this type, have been found to exist in the form of their *γ-lactones*; for example—

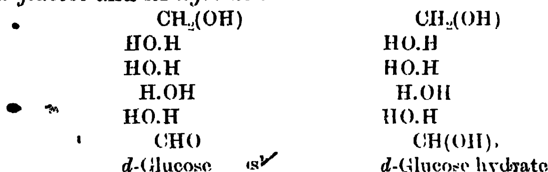


d-Gluconic acid.   *d*-Gluconic lactone.

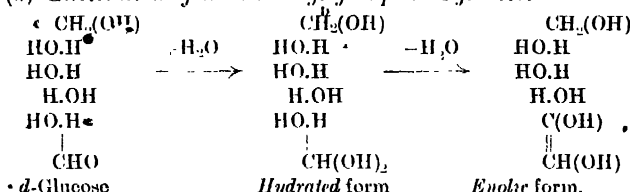
For this and other reasons, it is very likely that the hexoses themselves frequently exist in a γ-lactonic form, such as:



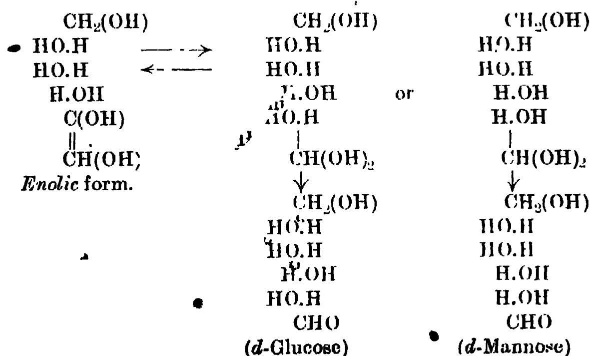
Let us then consider the possible isomerides resulting from *d-glucose* and its *hydrate*:



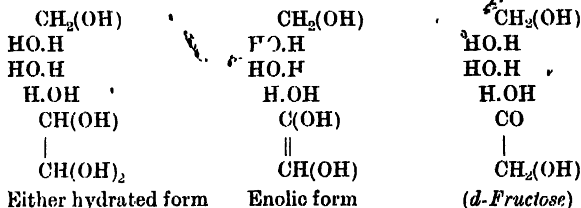
(*a*) *Enolization of the carbonyl group in d-glucose.*



The enolic form can now pass back to either of *three* carbonylic varieties, according to the manner in which water is split off and the new configuration of that carbon atom which, rendered *non-asymmetric* in the process of enolization, has again become *asymmetric*:—



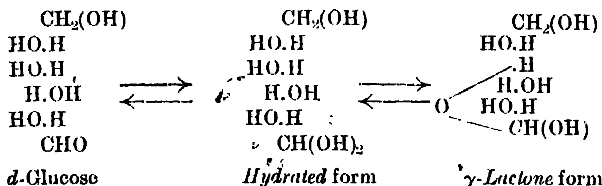
The third possible ketonic form is *d-fructose*, which results from elimination of water (in a different manner) from either of the new hydrated forms:



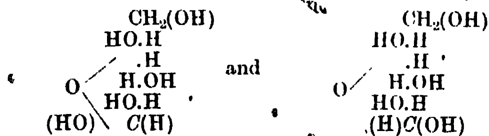
These enol-keto transformations, then, do not throw any further light on the three forms of *d-glucose* itself, but explain, incidentally, the production of *d*-mannose and *d*-fructose from *d*-glucose in presence of alkalies (p. 255), which are known to cause enolizing effects.

We must therefore turn to:

(*b*) *γ-Lactone formation from d-glucose.*



Now it will be seen that the lactonic form contains a new asymmetric carbon atom (that formerly in the aldehydic group). Consequently *two* optical isomerides of this form can exist:—



These, together with the simple aldehyde formula of *d*-glucose, furnish in all *three* possible forms of that substance.

It is not, however, considered very probable that these cor-

respond respectively to the known α-, β-, and γ-*d*-glucoses, but, in the opinions of Emil Fischer and Lobry de Bruyn, that *α-d-glucose* and *β-d-glucose* correspond to either of the lactonic forms above, whilst *γ-d-glucose* is an equilibrium mixture of the α- and β-varieties.

l-Glucose has not yet been found in nature, but has been prepared by reduction of *l*-gluconic lactone (from *l*-arabinose by Kiliani's reaction). It melts at 143°, and, when dissolved in water, gives a specific rotatory power $[\alpha]_D = -95 \cdot 5°$, which rapidly decreases to $[\alpha]_D = -51°$. Its *osazone* melts at 208°.

(*d-+l-*)*Glucose* results when equal quantities of *d-* and *l*-glucose are crystallized from water, or when *racemic* gluconic acid lactone is reduced. It is a syrup which furnishes (*d-+l-*) *glucosazone*, melting at 218°.

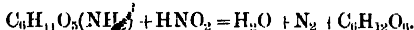
As is well known, glucose is estimated in general by its reducing action on Fehling's solution, the solution being made of such a strength (34·65 gms. $CuSO_4$: 200 gms. Rochelle salt: 600 c.c. NaOHaq. (20 per cent.) made up to one litre) that 200 c.c. are equivalent to 1 gm. of glucose or other hexose.

If no other optically active material is present, glucose may also be estimated polarimetrically.

d-Glucosamine, $C_6H_{11}O_5(NH_2)$, is a substance closely allied to glucose, occurring in the shells of many crustacea (lobsters and crabs), and also in mucus and other albuminous matter.

It exists in the shell as a cellulose *chitin*, and treatment of the latter with dilute acids gives the salts of glucosamine.

The free base melts at 105-110° with decomposition; it contains an aliphatic amino-group, which is readily replaced in the usual manner by hydroxyl on treatment with nitrous acid :



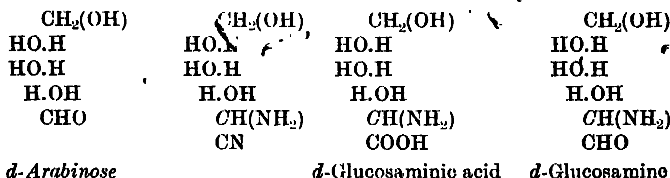
$$C_6H_{11}O_5(NH_2) + HNO_2 = H_2O + N_2 + C_6H_{12}O_6.$$

The product is a hexose known as *chitose*.

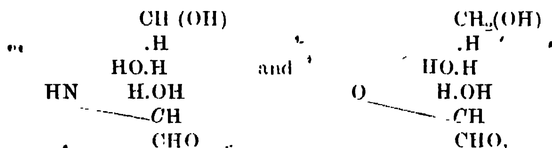
d-Glucosamine and phenylhydrazine react to form *d-glucosazone*, the amino-group disappearing. This indicates that the amino-group has replaced an hydroxyl radicle attached to the atom next to the aldehyde group.

This view is supported by E. Fischer and Leuchs' synthesis

of *d-glucosamine* from *d*-arabinose by addition of ammonium cyanide and subsequent hydrolysis of the nitrile group (compare the synthesis of *serin* from *glycolose*, p. 246).



The configuration of the new asymmetric atom is not known; if it were *dextro*-, *d*-glucose should result by treatment of *d*-glucosamine with nitrous acid, and if *lævo*-, *d*-mannose. Since neither is formed, but a new hexose *chitose*, Fischer has suggested that *d*-glucosamine and chitose respectively are possibly



the formulæ $C_6H_{13}O_5N$ (*d*-glucosamine) and $C_6H_{12}O_6$ (chitose) representing added molecules of water of crystallization.

d-Mannose occurs in many plants, but is by no means so widely distributed as grape sugar. It occasionally accompanies the latter in small quantities, whilst in the combined state it is found in certain classes of the celluloses, known from this fact as *mannoso-celluloses.*

It is best prepared by the action of dilute sulphuric acid on the mannoso-celluloses, and has also been obtained, in small yield and mixed with *d*-fructose as well as other products, when natural *d*-mannitol (p. 270) is carefully oxidized.

d-Mannose melts at 132°; with phenylhydrazine, it gives *d-glucosazone* (m.p. 210°). Reduction of *d*-mannose gives *d*-mannitol, and oxidation, the monobasic *d*-mannonic acid (p. 277), and dibasic *d*-mannosaccharic acid (p. 281).

l-Mannose resembles *d*-mannose in all respects save the sign of its optical activity, but has only been prepared by reduction of synthetic *l*-mannonic lactone.

(d- +l-)Mannose, formed by mixing the two components, by reduction of synthetic *racemic* mannonic acid, or by oxidation of *racemic* mannitol, melts at 132°, and forms *(d- +l-)glucosazone* (m.p. 218°).

d-Galactose is believed to occur free in nature in some kinds of honey, whilst combined with other bodies it is found—

(i) In a few *glucosides*, such as digitalin and vicin.
(ii) In the disaccharide *lactose* (with *d*-glucose).
(iii) In certain gums and celluloses (called therefrom *galactanes*).

It may be conveniently prepared from lactose or the galactanes by digestion with dilute sulphuric acid; and, synthetically, by reduction of *d*-galactonic lactone.

d-Galactose melts at 160°, and its *osazone* at 193°. Reduction converts it to *i-dulcitol* (p. 271), and oxidation to *d-galactonic* (p. 277) and *i-mucic acids* (p. 280).

l-Galactose was synthesized by the reduction of *l*-galactonic lactone. It melts at 163°, and its *osazone* at 195° (with decomposition).

(d- +l-)Galactose, also, is only known as a synthetic product; it melts at 144°, whilst its *osazone* is a yellow powder which melts and decomposes at 206°.

The remainder of the aldohexoses have only been prepared from their corresponding monobasic acid lactones. It will therefore suffice to tabulate them, with reference to their configurations and the acids from which they have been produced.

	Ref. on pp. 233-235.	*From.*	*M.p.*	*Osazone m.p.*
(Glucose *d*- and *l*-)	3 (*d*- & *l*-)	(See above, p. 254)	146°	210°
Gulose (*d*- and *l*-)	4 (*d*- & *l*-)	*d*- or *l*-Gulonic acid	Syrup	156°
Talose (*d*)	5 (*d*)	*d*-Talonic acid	Syrup	(gives *d-Galact-osazone*)
(Mannose *d*- and *l*-)	6 (*d*- & *l*-)	(See above)	134°	(give *Glucozazones*)
(Galactose *d*- and *l*-)	7 (*d*- & *l*-)	(See above)	160°	193°
Idose (*d*- and *l*-)	8 (*d*- & *l*-)	*d*- or *l*-Idonic acid	Syrup	(give *Gulosazones*)

B. KETOHEXOSES.

d-Fructose (*fruit-sugar*, *lævulose*), the most familiar member of this group, usually accompanies *d*-glucose in nature, when occurring uncombined with other substances. It is also, of course, combined with *d*-glucose itself in the widely distributed cane-sugar (p. 308). Moreover, *d-fructose* is a constituent of various complex nitrogenous compounds which are stored in the roots of many tuberous plants (notably in the *Solanaceæ*, *Compositæ*, *Liliaceæ*, and *Iridaceæ*—potatoes, dahlias, chicory, hyacinths, narcissi, etc.), and are present therein in exceptional abundance during the winter months. These bodies are termed *inulins*, and *d-fructose* results from them by treatment with dilute acids. This sugar also occurs in the urine of various carnivora.

d-Fructose may be produced by a bio-chemical process in the fermentation of *d*-mannitol with *Bacterium xylinum*, and chemically by hydrolysis ("inversion") of cane-sugar as well as of inulin, and by reduction of *d-glucosone*, the keto-aldehyde of which *d-glucosazone* is the diphenylhydrazone.

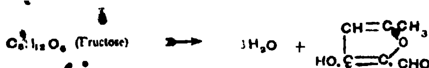
d-Fructose is a crystalline solid, not quite so soluble in water or alcohol as *d*-glucose, and melting at about 100°. Like *d*-glucose, it forms a monohydrate, and also exhibits *mutarotation*, its specific rotation falling from $[\alpha]_D = -106°$ to $[\alpha]_D = -93°$ after some little time.

With phenylhydrazine it yields *d*-glucosazone, and this proves its configurational relationship to the aldohexoses, especially *d*-glucose and *d*-mannose. For this reason, too, the *lævo*-rotatory fructose is termed *d-fructose*, in accordance with the convention maintained throughout.

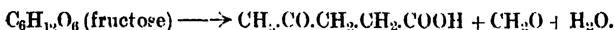
Reduction of *d*-fructose gives *d*-mannitol, whilst oxidation produces a variety of acids, none of which contain more than *four* carbon atoms. Amongst these are formic, oxalic, pyruvic, glycollic, tartaric, *d*-erythronic (pp. 273, 274), and trioxy-butyric acids.

Two reactions of *d*-fructose may serve again to emphasize the chemical distinctions between the aldohexoses and keto-hexoses :—

(i) Heated with dehydrating agents, such as oxalic or sulphuric acids, a certain quantity of α-methyl-β¹-oxyfurfuraldehyde is formed,



(ii) Prolonged boiling of fructose with dilute mineral acids yields lævulinic acid in quantity:


$C_6H_{12}O_6$ (fructose) ⟶ $CH_3.CO.CH_2.CH_2.COOH + CH_2O + H_2O$.

d-Fructose is fermentable by yeast; it forms alcoholates with the alkaline-earth and a few of the heavy metals.

l*-Fructose** (which is not fermentable by yeast) and *racemic* or (*d*- +*l*-) ***Fructose have only been prepared synthetically, and will be mentioned again in the next chapter (p. 286).

d-Sorbinose occurs in the berries of the mountain-ash or rowan tree, and has also been prepared artificially by the bacterial oxidation (*Bacterium xylinum*) of *d*-sorbitol (p. 270), and from *d-gulosone* (corresponding to *d*-gulosazone, p. 261).

It forms rhombic crystals which melt at 157°, and has $[\alpha]_D$ = *circa* – 40°. Reduction leads to *d*-sorbitol, and oxidation to oxalic, pyruvic, tartaric, and trioxybutyric, amongst other, acids.

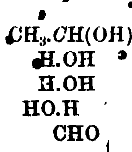
It is not fermentable by yeast.

l-Sorbinose and *racemic* (*d*- +*l*-)*Sorbinose* have been obtained artificially from their osazones, (*l*- and (*d*- +*l*-)gulosazones).

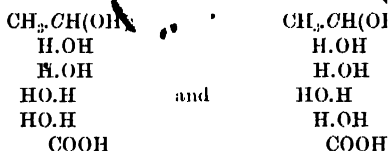
Formose is a synthetic ketohexose obtained by condensation of formaldehyde; it will be dealt with in chapter xv. (p. 286).

C. Methylhexoses.

α- and *β*- *Rhamnohexoses*, $CH_3[CH(OH)]_5.CHO$, have been prepared by Kiliani's reaction from the methylpentose *rhamnose*, which we found on p. 252 most probably to possess the configuration


$CH_3.CH(OH)$
H.OH
H.OH
HO.H
CHO

When *rhamnose* is treated with prussic acid and the product hydrolysed, two acids are formed which by repeated crystallization of their brucine salts can be separated, and correspond to the two formulæ :



The lactone of one acid (designated α-) possesses $[\alpha]_D = +86°$, that of the other (β-) acid has $[\alpha]_D = +43°$.

The α-lactone is reducible to *α-Rhamnohexose*, which melts at 180°, and has $[\alpha]_D = -61°$, its *osazone* melting at 200°.

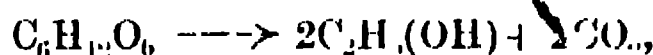
The β-lactone similarly furnishes *β-Rhamnohexose*, only isolated in the form of its *osazone*, which decomposes at about 200°.

D. Fermentation of the Hexoses.

The hexoses are susceptible to the action of numerous ferments, organized and unorganized (enzymes); the various fermentations are generally classified according to the products produced :—

(i) *Alcoholic Fermentation.*—This is propagated most effectively by yeast (containing the ferment *zymase*), and also by the fungi known as *Mycoderma*, *Schizomycetes*, and *Saccharomyces*. The action proceeds most rapidly between 30° and 35° C., higher temperatures destroying the ferment. Whilst the presence of nitrogenous bodies is necessary to the life of the ferment, other substances (such as various inorganic salts) act inhibitingly, owing to their toxic effect on the organisms.

The main reaction in this fermentation is the production of alcohol and carbonic acid,



but many other products are also formed (although in much smaller amount). Such are formic acid, acetic acid, aldehyde, glycerol, and most of the alcohols from propyl to hexyl, together with furfuraldehyde and traces of the higher aliphatic esters and acids.

All hexoses are not fermentable by yeast; indeed, the only members of this series susceptible to *zymase* appear to be *d-glucose*,

d-fructose, *d-mannose*, and *d-galactose*. This and other striking cases of selective fermentation by various ferments (compare the synthetic glucosides, chap. xvi., p. 301) have led Emil Fischer to the suggestion that a ferment and a sugar correspond roughly to a key and a lock, the key only responding to certain types of lock.

(ii) *Lactic Acid Fermentation.*—Certain bacteria present in sour milk, stale cheese, the mucus of the teeth, etc., exert a very different action on the hexoses to that of *zymase* and its co-workers. The chief outcome of the *lactic acid ferment* is the formation of two molecules of lactic acid from each hexose molecule :—



$$C_6H_{12}O_6 \longrightarrow 2CH_3.CH(OH).COOH.$$

According to the specific nature of the ferment acting, *dextro-*, *lævo-*, or *racemic* lactic acid may be formed.

Propionic, valerianic, and other acids are simultaneously formed, but in much less quantity.

(iii) *Butyric Acid Fermentation.*—When the lactic acid fermentation has proceeded for a long time, other kinds of bacteria are propagated, which produce butyric acid as the main product of fermentation of glucose :—



$$C_6H_{12}O_6 \longrightarrow C_3H_7.COOH + 2CO_2 + 2H_2.$$

(iv) *Mucous Fermentation.*—Finally, there remain another class of bacteria (including the *Bacteriædiphtheriæ*, *pneumoniæ crouposæ*, *Streptococcus*, and *tumescens*) which convert the sugars into gummy material (apparently of the usual polysaccharide formula $[C_6H_{10}O_5]_n$), also producing mannitol, lactic acid, carbon dioxide, and hydrogen.

VI. The Heptoses

No heptose has yet been found in nature, but as members of this series, as well as the octoses and nonoses, have been prepared by means of the Kiliani synthesis, it is of interest to give a brief account of a few members of this class.

A. Aldoheptoses.

Two stereoisomeric acids result when *d-glucose cyanhydrin* is saponified, and are known respectively as *α*- and *β*- *d-glucoheptonic acids*. They may be separated by crystallization from suitable solvents, or better by crystallization of their brucine salts, which show greater differences in solubility.

The *lactones* of these acids are reducible to the corresponding aldoheptoses, *α-d-glucoheptose* and *β-d-glucoheptose*.

α-d-Glucoheptose melts at 180-190°, and is *lævo*-rotatory ($[\alpha]_D = -20°$); its *osazone* melts at 193-195°.

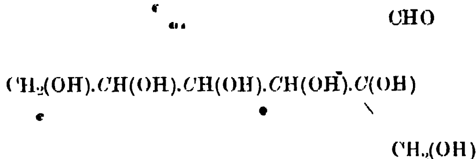
β-d-Glucoheptose has not been obtained crystalline; as might be expected in view of its configurational relationship with *α-d-glucoheptose*, its *osazone* is identical with that from the latter sugar.

The corresponding lactone from *d-mannose*, that of ***d-manno-heptonic acid***, furnishes *d-mannoheptose* by reduction with sodium amalgam. This sugar forms crystalline needles, melting at 134°. and with $[\alpha]_D = +85°$ (at first, afterwards decreasing to +69°). The *osazone* melts at 200°.

The *l-mannoheptose* has also been prepared from *l-mannoheptonic* lactone in the form of a *dextro*-rotatory syrup, and giving an *osazone* which melts at 203°.

The above sugars are reduced by sodium to the corresponding heptahydric alcohols, *α-* and *β-glucoheptitols*, and *d-* and *l-mannoheptitols*. Oxidation leads to the monobasic *α-* and *β-glucoheptonic acids* and the *d-* and *l-mannoheptonic acids*, and later to the dibasic *pentaoxypimelic acids*, $COOH.[CH(OH)]_5.COOH$.

B. KETOHEPTOSES.—These are not yet definitely known, but would be somewhat exceptional, owing to the presence of a branched carbon chain in the (synthetic) sugar molecule. For example, fructoheptose (from fructose) would possess the formula



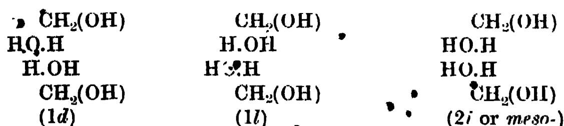
C. METHYLHEPTOSES.—*Rhamnoheptose* has been prepared from *rhamnohexose* in the usual manner; it is a syrup with weak *dextro*-rotatory power, and forms an *osazone* which melts at 200.

VII. ALCOHOLS RELATED TO THE DI-, TRI-, AND TETR-OSES

It is unnecessary to go further than to mention that *glycol*, $CH_2(OH).CH_2(OH)$, and *glycerol*, $CH_2(OH).CH(OH).CH_2(OH)$, are

the alcohols which correspond respectively to the Diose *glycolose* and to the Trioses *glycerose* and *dioxyacetone*. The properties and reactions of glycol and glycerol are familiar, and are described in elementary text-books of organic chemistry (*cf.* this series, part i., pp. 63, 110).

The alcohols related to the Tetroses (p. 248) are three in number, and are known as *erythritols*, $CH_2(OH).CH(OH).CH(OH).CH_2(OH)$. As shown on page 232, the three forms of erythritol are the *dextro-*, *lævo-*, and internally compensated or *meso*-varieties :—

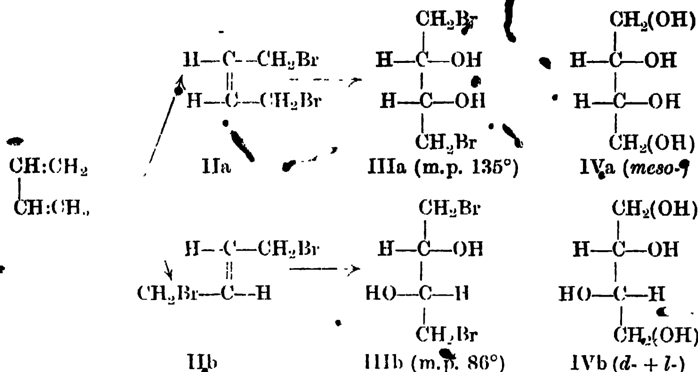


Of these, the optically active varieties have only been obtained by alkaline reduction of *l-threose* (which gives *l-erythritol*, m.p. 88° and $[\alpha]_D = +4°$) and of *d*-erythrulose (a ketose which yields *d-erythritol*, m.p 88° and $[\alpha]_D = -4°$).

The inactive *meso*-form (produced by reduction of *d-* or *l-erythrose*) occurs, however, in nature in many mosses and lichens as the ester of *orsellinic acid*, $C_8H_8O_4$.

It melts at 126°, and gives a *tetracetate*, m.p. 85°. Like most of the polyhydric alcohols, its *tetranitrate*, "*nitroerythritol*" (which is a solid, m.p. 61°), explodes when struck or suddenly heated.

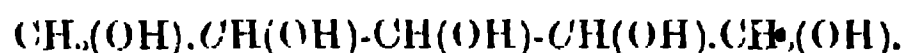
Both internally and externally compensated erythritols have been synthesized by Griner (1893) from the hydrocarbon *divinyl* (I), $CH_2:CH.CH:CH_2$. This yields two stereoisomeric *dibromides* (II) with bromine, which reacts additively with the conjugated diethenoid system in the usual manner and conformably with Thiele's theory. By oxidation with ice-cold permanganate solution, hydroxyl groups are added on to each unsaturated carbon atom, and the compounds (III) result. By treatment with aqueous alkali, one of these, which melts at 135°, gives *i-erythritol*, and the other, melting at 86°, gives *racemic* (*d-* + *l-*) *erythritol*, as would be expected from the fact that IIIa is known to be the "*cis-*" and IIIb the "*trans-*" isomeride.



The synthetic *i-erythritol* melts at 126°, and is in all respects identical with the naturally occurring alcohol; the *racemic* compound melts at 71°.

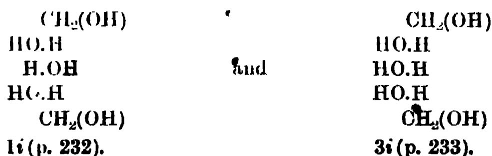
VIII. Alcohols related to the Pentoses

The stereoisomeric normal pentahydric alcohols of the formula $CH_2(OH).[CH(OH)]_3.CH_2(OH)$ are four in number (compare p. 232), and comprise two *meso*-, one *dextro*-, and one *lævo*- variety. They each contain only two asymmetric carbon atoms, the central carbon atom in the molecule being united to two chemically identical groups :—



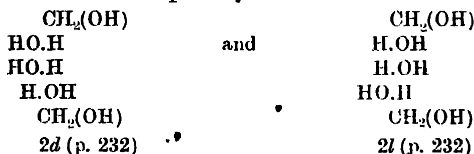
$$CH_2(OH).CH(OH)\text{-}CH(OH)\text{-}CH(OH).CH_2(OH).$$

Although this central group is non-asymmetric, if one of the two asymmetric atoms is of opposite configuration to the other, it is possible for the hydrogen and hydroxyl attached to the central atom to occupy either of two positions relative to those of the remaining groups, thus :—



Accordingly there are *two meso-* forms possible, and two are also known: *i-adonitol*, found in the alkaline reduction of the *riboses*, and corresponding to formula 1*i*, and *i-xylitol*, similarly produced from either of the *xyloses*, and possessing the structure 3*i*.

The remaining varieties of these alcohols are theoretically capable of existence in optically active forms :—



These are known as (the *d-* and *l-* forms of) *arabitol*, from their connexion with the best-known pentose, arabinose.

The common reduction product of *d-arabinose* and of *l-lyxose* is *d-arabitol* (formula 2*d*), whilst *l-arabitol* (formula 2*l*) is produced from *l-arabinose* or *d-lyxose*.

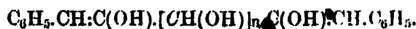
All these alcohols are exclusively artificial in origin, except *i-adonitol*, which is found in the plant pheasant's eye (*Adonis vernalis*).

Finally, reduction of the naturally occurring (glucoside constituent) *d-rhamnose* yields a methylpentitol, *d-rhamnitol*, which is probably a methyl homologue of *d-arabitol*.

These alcohols are quite similar in behaviour to the erythritols or hexitols, and are characterized as usual by the explosive nature of their pentanitrates. A few of their physical constants are given in the ensuing table.

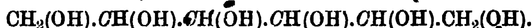
	Ref. on pp. 232, 233.	*M.p.*	[α]	*M.p. of dibenzal compound* *
i-Adonitol	1*i*	102°	—	165°
d-Arabitol	2*d*	103°	+7°	—
l-Arabitol	2*l*	102°	−5°	152° (monobenzal-compound)
i-Xylitol	3*i*	Syrup	—	175°
d-Rhamnitol	?	121°	11°	203°

* The polyhydric alcohols of the general formula $CH_2(OH).[CH(OH)]_n.CH_2OH$ condense readily with benzaldehyde to characteristic well-crystallized derivatives of the structure :—



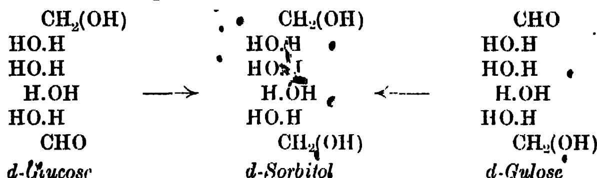
IX. Alcohols related to the Hexoses

As already shown in chapter xiii. (pp. 233-235), there are ten possible stereoisomeric modifications of the hexahydric alcohols:



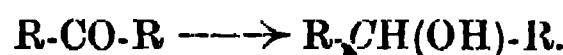
We shall only mention in detail three of these, namely, those produced in the reduction of *glucose, fructose, mannose, and galactose.*

Alkaline reduction of *d-glucose* produces for the greater part *d-sorbitol*, which must therefore have the configuration given below :—



Since it will be recalled that *d-gulose* (p. 239) differs from *d-glucose* merely in the relative positions of its alcoholic ($CH_2(OH)$-) and aldehydic (-CHO) groups, it is natural that reduction of this sugar should also yield *d*-sorbitol.

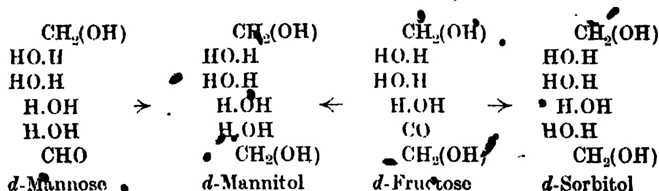
d-Sorbitol occurs in mountain-ash berries, and is also produced when *d-fructose* is reduced. In the latter case, however, reduction is accompanied by the formation of a new asymmetric carbon atom from the ketonic radicle :—



Consequently a second optically active alcohol is produced in equal amount at the same time: *d-mannitol.*

l-Sorbitol has been produced by reduction of *l-glucose* or *l-gulose.*

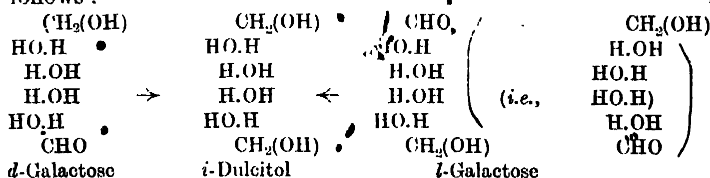
d-Mannitol, already mentioned as met with in the reduction of *d-fructose*, is similarly formed from *d-mannose*, and also occurs somewhat plentifully in the vegetable kingdom, especially in the manna-ash (*Fraxinus ornus*). Its formation from *d*-mannose and *d*-fructose (together with that of *d-sorbitol* from the ketose) is illustrated by the following diagram :—



l-Mannitol is produced when *l-mannose* is reduced.

Racemic (*d- l-*) *Mannitol* is important because of its connexion with the synthetic production of the sugars from formaldehyde, and it will accordingly receive further notice in the next chapter (pp. 286).

Finally, reduction of *d-* or of *l-galactose* produces the *meso*-alcohol *dulcitol*, which also occurs in certain plants (notably Madagascar manna). Its configuration must therefore be as follows :—



The sorbitols, mannitols, and dulcitols are sweet, well-crystallized compounds, quite soluble in water and alcohol, yielding the usual (hexa-)acetyl and -benzoyl derivatives, dibenzal compounds, and explosive hexanitrates ; their chief constants are given in the table below :—

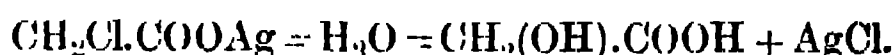
	Ref. on pp. 233-235.	*M.p.*	$[\alpha]^D$.	*M.p. of hexacetate.*	*M.p. of dibenzal-compound*
d-Sorbitol	3*d*	110°	weakly *d*-	Syrup	162°
l-Sorbitol	3*l*	110°	,, *l*-	Syrup	162°
d-Mannitol	6*d*	165°	+ 22° (with borax) (present)	119°	213°
l-Mannitol	6*l*	165°	− 22°	119°	213°
(*d*- + *l*-) Mannitol	—	168°	—	?	192°
i-Dulcitol.	7*i*	188°	—	171°	215°

X. Monobasic and Dibasic Acids related to the Dioses, Trioses, and Tetroses

A. Diose.—The first oxidation product of glycolose, *glycollic acid*, $CH_2(OH).COOH$, is well known as the lowest member of the

aliphatic oxyacids. It occurs in ivy-leaves and in unripe grape juice, and is found in the oxidation of not only glycolose, but also of ethylene glycol and alcohol with nitric acid.

It may be synthesized from acetic acid by boiling monochloracetic acid with dilute alkali (Kekulé, 1858), or merely by heating silver monochloracetate with water :—

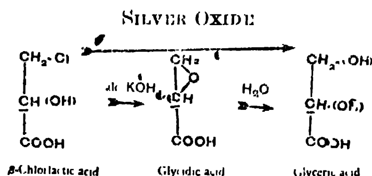


$$CH_2Cl.COOAg + H_2O = CH_2(OH).COOH + AgCl.$$

It was discovered by Strecker in 1848, in the action of nitrous acid on glycocoll.

The corresponding dibasic acid, *oxalic acid*, is too well known to require further remark.

B. Trioses.—*Glycerose* yields *glyceric acid*, $CH_2(OH).CH(OH).COOH$, as its first product of oxidation; this acid is also formed when glycerol is carefully oxidized with mercuric oxide or silver oxide, or when silver oxide acts on β-chlorlactic acid, $CH_2Cl.CH(OH).COOH$. If alcoholic potash is substituted for silver oxide in the last case, an ether acid corresponding to epichlorhydrin and glycide (chap. ii. p. 21) is produced :—



Glyceric acid is a syrupy liquid, which can be obtained in its optically active forms by the action of different ferments (*Penicillium glaucum*, for example, destroys the *d*-form and leaves the *l*-acid). The esters of the active acids have received much attention from the point of view of quantitative relations in optical activity.

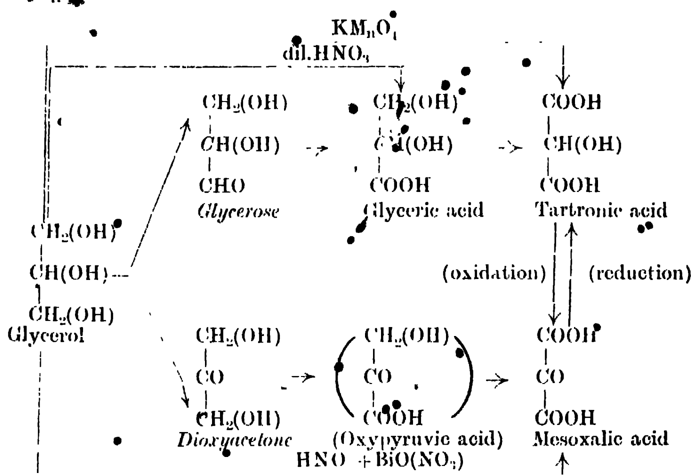
Dioxyacetone furnishes *mesoxalic acid*, $COOH.CO.COOH$, when carefully oxidized. The acid is also formed from alloxan (p. 195) and boiling baryta water, from dibrommalonic acid and silver oxide, or from glycerol by oxidation with nitric acid in presence

of bismuth oxynitrate (which forms insoluble bismuth mesoxalate and so removes the acid from possible further oxidation).

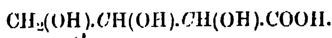
Mesoxalic acid is a deliquescent solid, and crystallizes with a molecule of water, which is very intimately combined, and is probably attached to the carbonyl group – COOH.C(OH)$_2$.COOH.

Reduction of mesoxalic acid with sodium amalgam produces *tartronic acid*, COOH.CH(OH).COOH, the dibasic acid corresponding to *glycerose.*

The relations between these various compounds are shown collectively in the next diagram :—

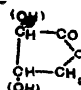


C. TETROSES. The first oxidation products of the *erythroses* and *threoses* are the trioxybutyric acids of the general formula



CH$_2$(OH).CH(OH).CH(OH).COOH.

These are syrups, which readily pass into crystalline γ *lactones* of the structure



Their configurations correspond to those of their parent tetroses and are thus as follows :—

	$CH_2(OH)$	$CH_2(OH)$	$CH_2(OH)$	$CH_2(OH)$
	HO.H	H.OH	HO.H	H.OH
	H.OH	HO.H	HO.H	H.OH
	COOH	COOH	COOH	COOH
	1*d*	1*l*	2*d*	2*l*
Acid :—	*l*-Threonic	*d*-Threonic	*d*-Erythronic	*l*-Erythronic
Lactone :— M.p.:			103°	104°
$[\alpha]_D$			−73°	+72°

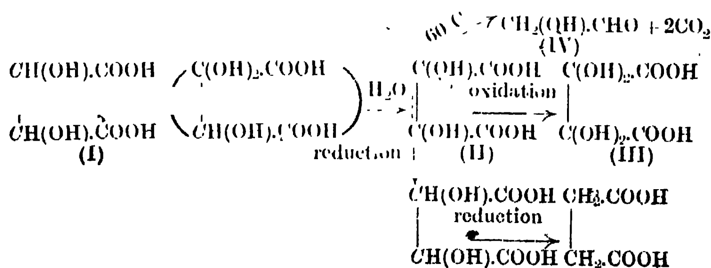
The dibasic acids corresponding to these are the three forms (*d*-, *l*-, and *i*- or *meso*-) of *tartaric acid*, which again are too common to need a detailed description here. *l-Threose*, which reduces to *l*-erythritol, also gives *l-tartaric acid* by oxidation, whilst *d*- or *l-erythrose* gives *i-tartaric acid* on oxidation, and *i-erythritol* on reduction.

The stereochemical connection between the *erythritols* and the *tartaric acids* is thus made clear.

We may refer again here to Fenton's work on the oxidation and other products of tartaric acid.

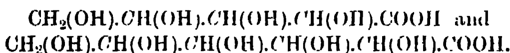
Tartaric acid (I), when oxidized by hydrogen dioxide in sunlight in presence of a ferric salt, is converted to *dioxymaleic acid* (II), which by further oxidation yields *dioxytartaric acid* (III), the sodium salt of which is so insoluble that it finds use in the quantitative estimation of that metal.

Reduction of *dioxymaleic acid* produces *racemic* tartaric acid and succinic acid; whilst on heating to 60° C. in aqueous solution (p. 246), *glycolose* (IV) is formed almost quantitatively :—



XI. Monobasic Acids related to the Pentoses and Hexoses

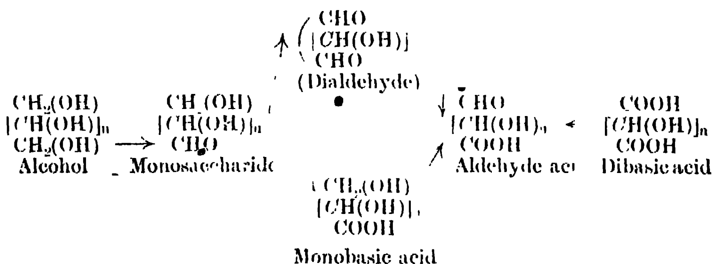
The first oxidation products of the aldopentoses and aldohexoses are respectively the optically active modifications of tetraoxy-*n*-valeric and of pentaoxy-*n*-hexoic acids :—



$CH_2(OH).CH(OH).CH(OH).CH(OH).COOH$ and
$CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH).COOH$.

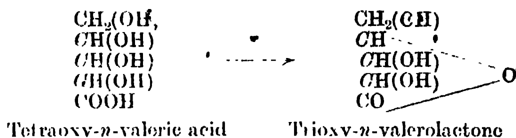
Intrinsically these are of the slightest interest, except for the fact that they are the very important intermediate phases in the transition from tetroses to pentoses, and from pentoses to hexoses. None of them occur in nature, and they have been obtained exclusively from the monosaccharides or from other saccharide acids.

The whole of the stages of oxidation of a typical sugar alcohol are tabulated below :—



Instances of all these products are familiar with the exception of the dialdehydes shown in brackets. These have never been prepared, and, indeed, it is probable that they are too unstable to exist as such, in view of the possibilities of intramolecular rearrangement, and of the known readiness with which groupings of the type $-CH(OH).CHO$ suffer intramolecular change. Hence it is most likely that, if the polyhydric dialdehydes result in any reaction, they at once pass into the lactones of the isomeric

monobasic acids. Even these, as a matter of fact, are extremely unstable in the free state, and pass into the corresponding *γ-lactones*.



Tetraoxy-*n*-valeric acid   Trioxy-*n*-valerolactone

The preparation of these acids from *aldopentoses* and *aldohexoses* has been achieved on the following lines :—

(i) Oxidation of the respective monosaccharides with bromine water.

(ii) Reduction of the lactones of the corresponding dibasic acids.

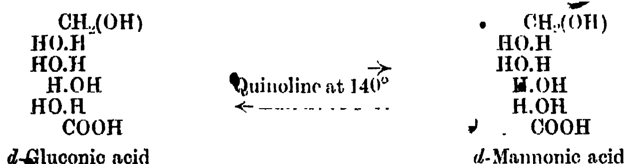
(iii) By Kiliani's reaction from (respectively) an aldotetrose or an aldopentose (the cyanhydrins of these latter sugars being hydrolysed by hydrochloric acid, when the lactones of the monobasic acids are produced).

Since the general symmetry of the molecule has not been altered, each aldose is represented by a corresponding polyoxymonocarboxylic acid, and the latter can therefore exist in the same number of stereoisomeric varieties as the parent sugars.

As already indicated, the free acids are unstable and pass into *γ-lactones*, which are optically active, crystalline compounds.

The *lactones* are reducible to the same *aldoses* from which the acids are formed by oxidation. The reduction is effected in weakly acid solution by sodium amalgam (Fischer); if more violent reagents (phosphorus and hydriodic acid) are employed, all the free hydroxyl radicles disappear and *γ-n-valerolactone* or *γ-n-caprolactone* (as the case may be) is produced.

An important stereochemical change takes place on heating the acids with strong aromatic bases (pyridine or quinoline) at 130°-140°. In this reaction the configuration of the asymmetric carbon atom next to the carboxyl group is affected, and an equilibrium mixture of two stereoisomeric acids results. Thus, if *d-gluconic acid*, corresponding to *d-glucose*, or *d-mannonic acid*, corresponding to *d-mannose*, is treated with quinoline at 140°, the same equilibrium-mixture of both acids is formed :—



Since a mixture of these acids can be separated by fractional crystallization of their salts with brucine (or other optically active bases), this reaction has proved of great utility, in the hands of Emil Fischer, in connection with the synthesis of various sugars.

Appended is a list of the acids of both pentose and hexose series, together with their lactones; since the physical properties of corresponding *d*- and *l*-forms are identical, it is unnecessary to refer to both of the optical antipodes in each case.

Tetraoxy-n-valeric acids (from the ALDOPENTOSES)

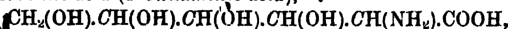
Acids.	*Ref. on pp. 232, 233.*	*By Kiliani's reaction from*	*Lactone. M.p.*	$[\alpha]_D$	*Reduction product of lactone.*
Ribonic	1	Erythrose.	76°	+18°	Ribose.
Arabonic.	2	Erythrose.	99°	+74°	Arabinose.
Xylonic	3	Threose.	92°	+83°	Xylose.
Lyxonic	4	Threose.	114°	+82°	Lyxose.

Pentaoxy-n-hexoic acids (from the ALDOHEXOSES)

Acids.	*Ref. on pp. 233-235.*	*By Kiliani's reaction from*	*Lactone. M.p.*	$[\alpha]_D$	*Reduction product of lactone.*
Gluconic	3	Arabinose	135°	+68°	Glucose.
Gulonic.	4	Xylose.	180°	+56°	Gulose.
Talonic.	5	Lyxose.			Talose.
Mannonic.	6	Arabinose.	153°	+54°	Mannose.
Galactonic	7	Lyxose.	92°		Galactose.
Idonic.	8	Xylose.			Idose.

Other monobasic acids connected with d-glucose.

***d*-Glucosaminic acid (*d*-Chitaminic acid),**


$CH_2(OH).CH(OH).CH(OH).CH(OH).CH(NH_2).COOH$,

is the oxidation product of *d-glucosamine* (p. 259), and, as already shown, has also been synthesized by E. Fischer from *d-arabinose* by addition to that pentose of ammonium cyanide, and subsequent hydrolysis.

It is a crystalline solid which chars at 250° without melting. It is weakly *lævo*-rotatory, and forms a crystalline *lactone*, which by reduction gives

d-glucosamine. The *nitrile* of the acid is formed by heating *d-glucosamine oxime* with acetic anhydride, and appears in the form of its *pentacetate* (Wohl's reaction).

Reduction of the acid by phosphorus and hydriodic acid at high temperatures produces *d-a-amino-n-hexoic acid* (*leucine*, chap. xi. p. 209).

d-Glucuronic acid, $CHO.[CH(OH)]_4.COOH$, may be taken as typical of the aldehyde acids (mentioned earlier in this section, p. 275), which stand between the monobasic acid and dibasic acid oxidation products of the aldohexoses. (Other acids of a similar nature have been prepared from *galactose* and *idose*.)

d-Glucuronic acid may be prepared by very cautious reduction of *d-saccharolactone* (p. 281); and it is also formed in the oxidation of glucose by mercuric oxide. Its interest, however, lies in the fact that it appears to find use as a kind of "carrier" for various organic materials of the most diverse types in their passage through the digestive organs. Thus, if such substances as terpene derivatives (menthol, camphor, etc.), phenols, aromatic amines, certain aldehydes, (*e.g.* chloral) and other carbonyl derivatives are administered internally to animals, they are excreted as condensation products of *d*-glycuronic acid: the condensation seems to be effected at the aldehydic radicle in the acid.

This peculiarity is adapted to commercial ends in the case of the pyrone dyestuff *euxanthone* (chap. vi. p. 93), which is isolated from Indian Mango leaves by means of the condensation product with *d*-glucuronic acid (*euxanthinic acid*) which is formed on digestion of the leaves by cows.

Euxanthinic acid is readily resolved into euxanthone and *d*-glucuronic acid by heating with 2% sulphuric acid at 100°.

d-Glucuronic acid is a sweet syrup, which readily forms the usual *γ-lactone*, *glucurone*, melting at 178°, and with $(\alpha)_D = +19°$.

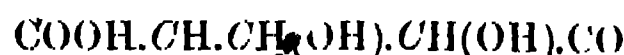
The *lactone* is reducible to *d*-gluconic acid and *d*-glucose, whilst oxidation yields *d*-saccharic acid. When distilled with aqueous hydrochloric acid, a considerable amount of *furfuraldehyde* is formed, and when submitted to the bacteria present in decaying flesh, glucurone is converted almost quantitatively to *l-xylose*.

XII. Dibasic Acids related to the Pentoses and Hexoses

With the appearance of two carboxyl groups in place of the radicles $CH_2(OH)$ – and – CHO of the aldose molecule, the asymmetry of the molecule becomes of the same general type as that in the polyhydric alcohols already described, in which the necessarily non-asymmetric carbon atoms are contained in the two primary alcohol residues $CH_2(OH)$ – and – $CH_2(OH)$.

Consequently the number of asymmetric forms of the dibasic acids resulting from the aldopentoses (4) and from the aldohexoses (10) is the same as in the corresponding normal pentahydric and hexahydric alcohols. Therefore it is unnecessary to recount the various individual configurations of these compounds, which may be gathered from a consideration of the respective alcohols to which they are related through the aldoses (see chap. xiii. pp. 232-235; this chapter, pp. 268 and 270).

The dibasic acids under review are the various forms of *trioxyglutaric acid*, $COOH.[CH(OH)]_3.COOH$, (from the aldopentoses), and *tetraoxyadipic acid*, $COOH.[CH(OH)]_4.COOH$ (from the aldohexoses). They are formed by oxidation, by means of dilute nitric acid, of either the respective monosaccharides, the monobasic acids of the latter, or the polyhydric alcohols to which they correspond. They are frequently crystalline, although some members of the class have only been obtained as syrupy liquids. They readily pass into *γ-lactonic acids* of the respective formulæ





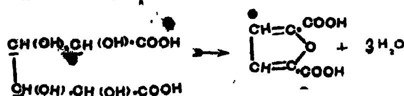
and





Continuous reduction of the lactones yields the corresponding aldehyde- and alcohol-monobasic acids, and finally the corresponding monosaccharides and their alcohols, whereas the acids themselves, by vigorous hydrogenation with phosphorus and hydriodic acid, give respectively *n-glutaric acid*, $COOH.[CH_2]_3.COOH$, and *n-adipic acid*, $COOH.[CH_2]_4.COOH$.

The dibasic acids of the *aldohexose* series are distinguished by their transformation (in varying degrees of readiness) to *furfurane-αα¹-dicarboxylic acid* when heated under pressure with aqueous hydrochloric acid:—



The characteristics of the varieties of *trioxyglutaric acid* are as follows :—

Acid.	*Ref. on pp. 232, 233.*	*M.p.*	$[\alpha]_D$	*Lactonic Acid. M.p.*	*Corresponding Alcohol.*	*Corresponding Pentose.*
Ribotrioxyglutaric.	1*i*	(Only as lactone).		170°	*i*-Adonitol.	*d*- & *l*-Ribose.
d-Trioxyglutaric.	2*d*	128°	+23°	?	*d*-Arabitol.	*d*-Arabinose. *l*-Lyxose. *d*-Rhamnose.
l-Trioxyglutaric.	2*l*	127°	−23°	?	*l*-Arabitol.	*l*-Arabinose. *d*-Lyxose.
Xylotrioxyglutaric.	3*i*	152°	–	Amorphous.	*i*-Xylitol.	*d*- & *l*-Xylose.

It will be noted that oxidation of *d*-Rhamnose leads to the production of *d*-trioxyglutaric acid, the methyl group disappearing.

As in the case of the corresponding alcohols, we shall only mention the dibasic acids connected with *d-glucose*, *d-fructose*, *d-mannose*, and *d-galactose*, in the division of the hexose acids.

d-Saccharic acid, corresponding to *d-glucose*, is also produced in the oxidation of dextrin, cane-sugar, maltose, and many other carbohydrates. It has been oxidized to *d-tartaric acid* (together with oxalic acid as a by-product).

d-Mannosaccharic acid is the dibasic acid corresponding to *d-mannose*. *Racemic tartaric acid* has been obtained from it by oxidation. The *racemic* mannosaccharic acid is important in connection with the synthesis of *glucose*, *fructose*, and *mannose* from formaldehyde (see chap. xv. p. 291).

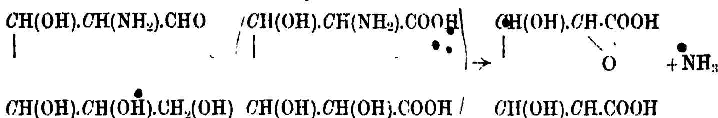
Mucic acid is produced when galactose, lactose, *d*-rhamnose carboxylic acid (*d*-rhamnohexonic acid), and many naturally occurring gums are oxidized.

It is remarkable for the ease with which it is transformed into derivatives of the furfurane series in accordance with the general reaction mentioned earlier in this section (p. 279).

Whilst it yields the *furfurane-αα¹-dicarboxylic acid* with hydriodic acid, when distilled alone *pyromucic acid* (*furfurane-α-carboxylic acid*) is produced, and carbon dioxide eliminated; on the other hand, when heated with sulphides of the alkaline earths or alkali metals, *thiophene-α-carboxylic acid* is the main product, and destructive distillation of ammonium mucate results in the production of *pyrrol*.

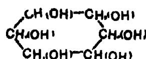
Acid.	*Ref. on pp. 233-235.*	*M.p.*	$[\alpha]_D$	*Lactonic Acid. M.p.*	$[\alpha]_D$	*Corresponding Alcohol.*	*Corresponding Hexoses.*
d-Saccharic.	3*d*	100°	+22°	130°	+42°	*d*-Sorbitol.	*d*-Glucose. *d*-Gulose.
d-Mannosaccharic.	6*d*	Syrup.	+1°	192°	+204°	*d*-Mannitol.	*d*-Mannose.
(*d*- + *l*-) Mannosaccharic.	-	Syrup.	–	185°	–	(*d*- + *l*-) Mannitol.	(*d*- + *l*-) Mannose.
i-Mucic.	7*i*	225°	-	Syrup	–	*i*-Dulcitol.	*d*-&*l*-Galactose.

When *d-glucosamine* (or *d-glucosaminic acid*) is oxidized, a *dioxytetrahydrofurfurane dicarboxylic acid* known as *isosaccharic acid* (*m.p.* 185°, $[\alpha]_D = +46°$), is formed (and not a tetraoxyadipic acid, as in the case of *glucose* and the other aldohexoses) :—



XIII. The Cycloses or Cyclic Hexoses

The molecular formula $C_6H_{12}O_6$, which is possessed by so many possible aliphatic isomerides of a pentahydroxy-aldehyde or pentahydroxy-ketone-like nature is shared by some of a cyclic structure, namely, that of *hexahydrohexaoxybenzene* (*Hexaoxycyclohexane*) :—



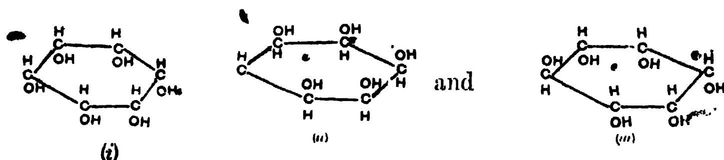
As a matter of fact, certain naturally occurring substances have been proved to possess this structure, and it is interesting to add that these compounds are also sweet tasting and in some cases optically active, thus closely resembling the aliphatic or true monosaccharides.

The three cyclic sugars which are known to possess the above cyclic formula are termed *inosites* ; one of them is *dextro-*, a second *lævo*-rotatory, and the third inactive.

Now it is obvious that compounds of this type do not possess molecular asymmetry of the usual kind ; but if the steric formula

$C_6H_6(OH)_6$ be examined, it will be seen that the hydroxyl groups may lie on either side of the plane of the carbon ring-system.

For example we may have :—



Here (i) is a symmetrically arranged molecule, *i.e.* it is identical with its mirror image ; but (ii) and (iii) are mirror-images of each other, and non-superposable (although this does not appear clearly from a plane illustration).

We may summarize the possible forms, then, by considering the number of hydroxyl groups on the "upper" side of the carbon-ring plane in diagrams similar to the above :—

	No. of hydroxyl groups.	*No. of forms.*	
(*a*)	0	1	Optically inactive.
(*b*)	1	1	Optically active.
(*c*)	2	3	Optically inactive.
(*d*)	3	3	Optically inactive.
(*e*)	4	3	Optically inactive. [identical with (*c*)].
(*f*)	5	1	Optically active [the optical antipode of (*b*)].
(*g*)	6	1	Optically inactive [identical with (*a*)].

There are thus seven distinct possibilities of optically inactive (*anti-* or *meso-*) forms, and two of enantiomorphic optically active varieties.

Evidently, then, the *d-* and *l*-forms of *inosite* correspond to configurations (ii) and (iii) in the above diagram (or to (*b*) and (*f*) in the table ; but, although *inactive inosite* is known to be a non-resolvable or *meso*-compound, it is not really known to which of the classes (*a*), (*c*), or (*d*), it belongs ; it is generally represented in the simplest possible manner, *i.e.* as in formula (i) above.

i-Inosite is found in unripe seeds of various *Leguminosæ* (peas and beans), and occasionally occurs in abnormal secretions of animal muscles. It melts at 225°, and is oxidized by nitric acid or other reagent to a mixture of oxyquinones.

d-Inosite occurs in the juices of certain tropical pines and rubber trees in the form of a monomethyl ether, *pinite*, $C_6H_6(OH)_5(OCH_3)$; it is isolated by heating with hydriodic acid as in the usual Zeisel reaction. It melts at 247° and sublimes; it possesses the specific rotatory power $[\alpha]_D = +65°$.

l-Inosite is found similarly, as a monomethyl ether, *quebrachite*, in the bark of the quebracha tree. It melts at 247°, and sublimes shortly after; its specific rotatory power is $[\alpha]_D = -65°$.

A few other modifications of *hexaoxyhexahydrobenzene* have also been found in nature, and also some of the lower *polyoxyhexahydrobenzenes*.

The more important of these are:—

	Formula.	*M.p.*	$[\alpha]_D$	*Source.*
Quercite	$C_6H_7(OH)_5$	235°	+24°	Acorns.
Quinic acid	$C_6H_7(OH)_4COOH$	162°		Cinchona bark.
Phloroglucite	$C_6H_9(OH)_3$	184°	...	Synthetic.
Quinite	$C_6H_{10}(OH)_2$	144°	-	Synthetic.
Hexahydrophenol	$C_6H_{11}(OH)$	15°	(b.p. 164°)	Synthetic.

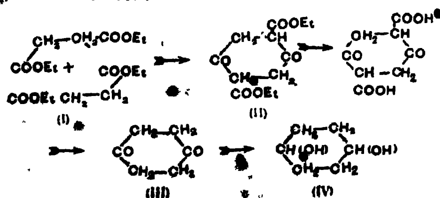
There are 16 possible configurations of *quercite* (6 pairs of enantiomorphs, and 4 *meso*-forms), but it is not known to which the natural product should be assigned. It is unattacked by zymase, and is oxidized by nitric acid to, amongst other products, mucic acid and (*d*- +*l*-) trioxyglutaric acid.

Quinic acid, which is found associated with cinchonine and quinine in cinchona bark, is a carboxylic derivative of the next lower cyclose $C_6H_8(OH)_4$. It yields several common aromatic compounds on distillation, such as phenol, salicylic aldehyde, and benzoic acid. It is oxidized to quinone by manganese dioxide and sulphuric acid, and reduced to benzoic acid by phosphorus and hydriodic acid.

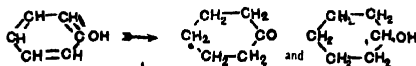
The remaining members of this class have only been prepared artificially.

Phloroglucite results when phloroglucinol is reduced with sodium amalgam.

Quinite (IV) was synthesized by Baeyer by alkaline reduction of *p*-diketohexamethylene (III), which he had previously obtained from ethyl succinosuccinate (II) by the action of concentrated sulphuric acid. The latter compound is produced by the Claisen condensation from diethyl succinate (I) and sodium ethoxide:—



Finally, *hexahydrophenol* is most readily produced by the reduction of phenol vapour with hydrogen in presence of finely-divided nickel at 200° (Sabatier and Senderens). *Cyclohexanone* is produced at the same time :—



If the crude product is re-hydrogenated in presence of nickel at 170°, pure *cyclohexanol*, a viscous liquid boiling at 164°, results, whilst if the mixture is passed (in the form of vapour, and without addition of hydrogen) over copper turnings at 320°, the whole is converted to *cyclohexanone*, a more mobile liquid, b.p. 155°.

CHAPTER XV

THE CARBOHYDRATES: SYNTHESES IN THE MONOSACCHARIDE SERIES

I. General

THE fermentation by yeast of ordinary cane-sugar (or rather the mixture of grape sugar and fruit sugar obtained from it by hydrolysis) was exhaustively studied by Lavoisier, who attempted to recombine the products of fermentation (carbon dioxide and alcohol) and reproduce the sugar. Ever since this period, numerous attempts have been made from time to time to solve this attractive problem, but since its extraordinary difficulty was not realized until a much later date, the earlier essays at sugar synthesis were of a haphazard nature and were practically all without result.

It is nevertheless interesting to remark that, according to van't Hoff, Lavoisier's synthesis should, from a theoretical and physico-chemical standpoint, be feasible; it has, however, not yet been carried out successfully. Van't Hoff assumed that ferment action was a catalytic change of a reversible nature, and that its usual course (leading to complete decomposition of the sugar) was followed as a result of the removal of the (gaseous) carbon dioxide from the reaction system. Consequently, by the law of mass-action, if the constituents could be maintained in a homogeneous system (*i.e.* both in the liquid state) in presence of zymase, sugars should result.

We need not refer to the various ineffective, although interesting, attempts to achieve the synthesis in question (from hydrogen, carbon dioxide, methane, *etc.*—and in divers of which the auxiliary aid of ferments, electrolysis, or the silent electric dis-

charge was invoked), but will pass on to the successful syntheses, in all of which an aldehyde (most often formaldehyde or acrolein) has served as a starting point. The chief of these are as follows :—

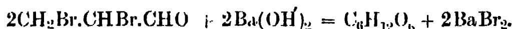
(i) Butlerow (1861) heated *trioxymethylene* (a tripolymeride of formaldehyde) with milk of lime, and produced a fermentable syrup, resembling a sugar, which he termed "*methylenecitan*," and showed to possess the formula $C_6H_{12}O_6$.

(ii) Loew (1885) used *formaldehyde* itself with milk of lime, and obtained a similar fermentable sugar-like syrup, known as *formose*.

(iii) Using magnesia in place of lime, Loew (1889) produced a third syrup of similar nature to the preceding, which he called *methose*. Both of Loew's products corresponded to the molecular composition $C_6H_{12}O_6$.

(iv) Emil Fischer showed in 1887, that *crude glycerose* is transformed almost completely to a syrup of the composition $C_6H_{12}O_6$ in presence of dilute alkalies. This syrup he termed *a-acrose*.

(v) Fischer also obtained *a-acrose* from acrolein dibromide and cold dilute aqueous baryta water :—



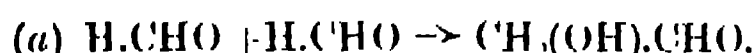
$$2CH_2Br.CHBr.CHO + 2Ba(OH)_2 = C_6H_{12}O_6 + 2BaBr_2.$$

He produced evidence, moreover, to prove that α-acrose was one of the constituents of the earlier synthetic products (*methylenecitan* and *formose*).

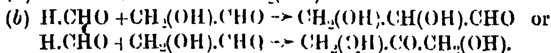
Now *α-acrose* was found to give (*d*-+*l*-) *mannitol* on reduction, whilst fermentation with yeast resulted in an almost fifty per cent. yield of *l-fructose*. Since it is a well-known fact that a ferment usually consumes only one optical artipode from a racemic mixture, it is evident that *α-acrose* is simply *racemic fructose*.

Its production is, therefore, the result of a series of "aldol condensations" :—

(i) From formaldehyde—

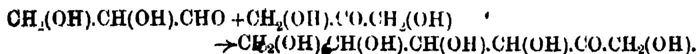


(*a*) $H.CHO + H.CHO \rightarrow CH_2(OH).CHO.$



(*b*) $H.CHO + CH_2(OH).CHO \rightarrow CH_2(OH).CH(OH).CHO$ or
$H.CHO + CH_2(OH).CHO \rightarrow CH_2(OH).CO.CH_2(OH).$

(ii) From *crude glycerose* —



$$CH_2(OH).CH(OH).CHO + CH_2(OH).CO.CH_2(OH) \rightarrow CH_2(OH).CH(OH).CH(OH).CH(OH).CO.CH_2(OH).$$

It is obvious, therefore, that either *glycerose* or *dioxyacetone* may be formed by the aldol condensation of formaldehyde; these condense further to a member of the hexose series. Similarly, *crude glycerose*, which (p. 247) is also a mixture of glycerose and dioxyacetone, yields the same product, *d*-+*l*-fructose.

α-*Acrose* has thus come to serve as the starting point for the syntheses of all the hexoses, pentoses, and tetroses so far carried out. This work is pre-eminently due to Emil Fischer, who spent many years on the problem before proceeding to the study of the purines and polypeptides (already outlined in chapters x. and xi.). Other names of importance in this field, which has been assiduously cultivated from 1887 onwards, are those of Tafel, Leuchs, Lobry de Bruyn, Kiliani, Wohl, Ruff, and Fenton.

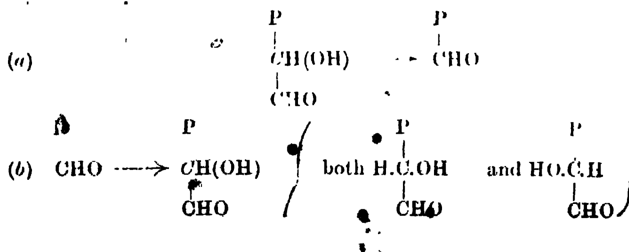
We will review the general methods used in the transformation of α-*acrose* into the different individual monosaccharides, before describing the syntheses of each separate class. We may in some measure classify the experimental methods involved by grouping them as follows :—

I. *Transformation from one class of monosaccharides to the next (higher or lower)* :—

(*a*) Degradation of a (primarily synthetic) monosaccharide to the corresponding sugar of the next lower series by Wohl's or Ruff's processes (p. 228) constitutes a synthesis of the lower sugar which is formed.

(*b*) Elevation of a (primarily synthetic) sugar to the corresponding members of the next higher series by Kiliani's reaction (p. 227) has also been of frequent service.

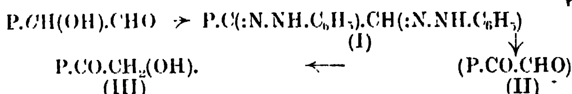
Whereas, however, the degradation method gives a definite stereochemical synthesis in all cases (since no fresh asymmetric centres are introduced), the Kiliani method involves the production of a new asymmetric carbon atom, which will possess in general both possible configurations, so that an equal quantity of two stereoisomeric sugars is the net result :—



If, however, the configuration of one of the latter products is known by an independent synthesis, that of the other follows; otherwise the Kiliani synthesis is stereochemically incomplete.

II. *Transformation from an aldose to a ketose of the same series.*

This has always been achieved by producing the *osazone* of the *aldose* (I), and converting it by reduction of the corresponding *osone* (II) to the *ketose* (III):—

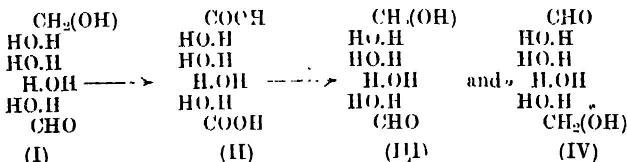


III. *Transformation from one aldose to another of the same series.*

This has been carried out by utilizing either of two methods:—

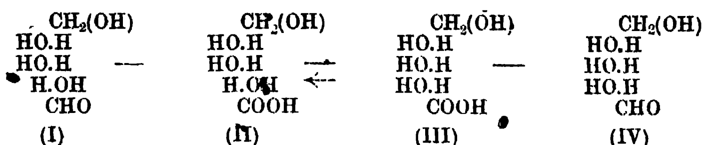
(i) Starting with a synthetic sugar, this is oxidised to the corresponding dibasic acid. Reduction of this (in the form of its lactone) produces a mixture of the original sugar and a new one, related to the other in that its $CH_2(OH)$ – and –CHO groups are in an inverse position to those (CHO – and – $CH_2(OH)$), of the original synthetic sugar.

Thus, taking synthetic *d-glucose* (I), this may be oxidized to *d-saccharic acid* (II), the lactone of which reduces to an equimolecular mixture of *d-glucose* (III) and *d-gulose* (IV). *d-Gulose* is thus proved to have the configuration shown in formula IV:—



(ii) A synthetic aldose may be oxidized to the corresponding monobasic acid. It is known (p. 276) that the latter acid, when heated at 130°-140° with quinoline, will suffer partial racemisation of the asymmetric carbon atom adjacent to the carboxyl group, an equilibrium mixture of the original acid with a new stereoisomeric acid being produced. The mixture may be separated by methods described below, and the new acid reduced to its corresponding *aldose*, which is thus synthetically prepared.

For example, synthetic *d-arabinose* (I) is oxidized to *d-arabonic acid* (II), which, heated with quinoline at 130°-140°, gives a certain proportion of *d-ribonic acid* (III): reduction of the latter, when freed from the accompanying *d*-arabonic acid, gives *d-ribose* (IV):—



IV. *Resolution of inactive synthetic sugars.*

The racemic products obtained in the first instance from formaldehyde, etc., have been resolved into their components by the following methods :—

(i) *Biochemical.*—The synthetic sugars, as such, are submitted to the action of given enzymes or ferments, some of which destroy one optical form, and others the opposite variety, of the sugar. The action of different ferments is excessively selective, as has been already pointed out (p. 265); but no definite rule has yet been discovered by which the fermentability of a sugar of given configuration may be predicted.

Roughly speaking, the *d-hexoses* (*d*-glucose, *d*-mannose, *d*-galactose, *d*-fructose) are destroyed by yeast ferment, whilst the *l*-stereoisomers are unattacked.

(ii) *Chemical.*—The acid oxidation products of the sugars may be combined with an optically active base, and the resulting mixture of two optically heterogeneous salts submitted to fractional crystallization.

Here, again, little is known of the rules governing the solubility of salts of acids of enantiomorphous configuration. As a qualitative rule which has but few exceptions, however, it is found that an acid in which the asymmetric atom next to the carboxylic radicle has the configuration I. yields sparingly soluble salts with quinine, strychnine, or brucine; whilst that in which the adjacent asymmetric carbon atom has the enantiomorphic disposition II., generally gives sparingly soluble salts of cinchonine or cinchonidine :



V. *Synthesis of the alcohols and acids genetically connected with the monosaccharides.*

Since the sugars can be reduced to the corresponding alcohols by sodium amalgam, whilst aldoses yield the corresponding mono- and di-basic acids by suitable oxidation, and since either kind of

acid can be reduced to the corresponding aldoses or alcohols, as well as (in the case of dibasic acids) to the aldehyde acids, it follows that, once a sugar or a corresponding monobasic acid or a corresponding dibasic acid has been synthesized, the synthesis of the complete series of derivatives ensues as a matter of course.

We will now examine in some detail the application of the foregoing methods to the synthesis of the more important individual hexoses.

II. Syntheses of the Hexoses

A. Glucose, Fructose, and Mannose.

(i) *d*- (and *l*-) *Mannose.* As already stated, reduction of synthetic *α-acrose* produces racemic mannitol, which, when reoxidized, furnishes firstly (*d*- +*l*-) *mannose* (a synthesis of this substance), and secondly (*d*- +*l*-) *mannonic acid.* The latter acid is separated into its active modifications by fractional crystallization of the brucine salts, and reduction of these leads respectively to *d*- (and *l*-) *mannose.*

(ii) *d*- (or *l*-) *Glucose.* The active *d*- or *l*- mannonic acids undergo partial racemization of one asymmetric carbon atom in the manner described above (p. 288), when heated with quinoline to 140°. The resulting acids are respectively *d*- and *l-gluconic acids*, and reduction of the lactones of the latter furnishes *d*- and *l-glucose.*

(iii) *d*- (or *l*-) *Fructose.* *d*-Mannose and *d*-glucose both yield *d-glucosazone* when treated with excess of phenylhydrazine, and the *d-glucosone* resulting from this compound by treatment with dilute aqueous sulphuric acid is reduced by sodium amalgam to *d-fructose.*

l-Fructose is similarly synthesized from the *osazone* of either *l-glucose* or *l-mannose*, and also results directly when *α-acrose* is fermented with yeast.

B. Gulose and Sorbinose.

(i) *d*- (or *l*-) *Gulose.* *d*- (or *l*-) *Gluconic acids* (by intramolecular rearrangement of synthetic *d*- (or *l*-) mannonic acids respectively,

or by oxidation of synthetic *d*- (or *l*-) glucose) are oxidized further to the dibasic *d*- (or *l*-) *saccharic acids*. Reduction of these produces an equi-molecular mixture respectively of *d*-gluconic and *d-gulonic acids*, or of *l*-gluconic and *l-gulonic acids*. The mixture of two acids may be separated in the usual way, and the pure *d*- (or *l*-) *gulonic acid* reduced to *d*- (or *l*-) *gulose*.

(ii) *d*- (or *l*-) *Sorbinose*. *d*- (or *l*-) *Gulosazone* yields the unstable *d*- (or *l*-) *gulosone* by acid hydrolysis, and the latter can then be reduced to *d*- (or *l*-) *sorbinose*.

The racemic forms of these different sugars can be synthesized simply by crystallization of equal quantities of the synthetic *dextro*- and *lævo*- forms.

The accompanying table illustrates the synthesis of the sugars of the *mannose* and *glucose* series (to which correspond respectively the alcohols *mannitol* and *sorbitol*, and the *mannosaccharic* and *saccharic acids*).

Dibromacrolein or *Formaldehyde* or *Crude Glycerose*

↓

α-**ACROSE**

↓

(*d*- + *l*-) Mannitol

↓

(*d*- + *l*-) Mannose

↓

(*d*- + *l*-) Mannonic Acid

|

l-Gluconic acid ← *l*-Mannonic acid ⟷ *d*-Mannonic acid → *d*-Gluconic acid ⇅ *d*-Saccharic acid ⇅ *d*-Gulonic acid

l-Gluconic acid → *l*-Glucose → *l-Glucosazone* → *l*-Fructose

l-Mannonic acid → *l*-Mannose → *l-Glucosazone*

d-Mannonic acid → ***d*-MANNOSE** → *d-Glucosazone*

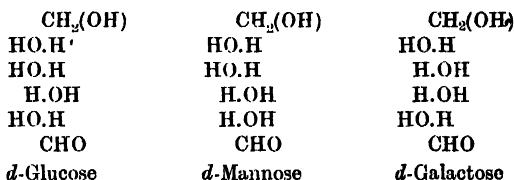
d-Gluconic acid → ***d*-GLUCOSE** → *d-Glucosazone* → ***d*-FRUCTOSE**

d-Gulonic acid → *d*-Gulose → *d-Gulosazone* → *d*-Sorbinose

C. Galactose, Idose, and Talose.

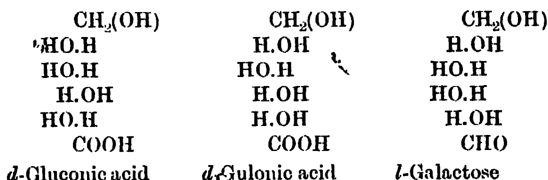
The syntheses of the remaining hexoses depend on a somewhat more complicated series of reactions; this is owing to the fact

that whilst the *glucose* and *mannose* series differ stereochemically only as regards the asymmetric atoms next to the aldehyde group, *galactose* differs from either of the former types in the configuration of the *third* asymmetric atom (counting from the aldehydic radicle).



d-Glucose *d*-Mannose *d*-Galactose

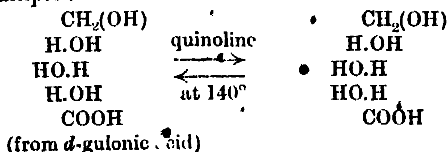
The syntheses all start, therefore, from the *gulonic acids*, which possess an " inverted " configuration to those of the *gluconic acids*, and thus have the two asymmetric atoms adjacent to the *alcoholic* group in the configuration necessary for the galactoses. Thus:



d-Gluconic acid *d*-Gulonic acid *l*-Galactose

(i) *d*- (or *l*-) *Galactose.* To convert the remaining two asymmetric atoms in the gulonic acids to the desired relative configurations it is necessary to degrade these compounds to the corresponding pentoses (thereby destroying one undesired atomic centre of asymmetry). The resulting monobasic pentose acid is then heated with quinoline to 140°, and thereby partly changed to an isomeric acid, in which the *three* asymmetric atoms are of suitable configuration for our purpose.

For example:



(from *d*-gulonic acid)

Kiliani's reaction is then applied to the pentose obtained by reduction of the lactone of the new acid, and two sugars result, one of which has all *four* asymmetric carbon atoms in the assumed configuration for *l-galactose* (if *d-gulonic acid* has been the original acid used).

Thus, in the synthesis of *d-galactose*, Fischer commenced with *l-gulonic acid*, degraded this by Wohl's reaction to *l-xylose* (the corresponding pentose), and oxidized the latter to *l-xylonic acid*, which was heated with quinoline at 140°. Reference to the table of pentose-configurations (chap. xiii, p. 232) will show that by "optical inversion" of the asymmetric atom next to the carboxyl group in *l*-xylonic acid, a stereoisomer whose configuration corresponds to *d-lyxonic acid* is formed.

The mixture of *l-xylonic* and *d-lyxonic acids* was separated by crystallization of their strychnine salts, and the corresponding *d-lyxonic lactone* reduced to *d-lyxose.*

On applying Kiliani's reaction to *d*-lyxose, a mixture of *d-galactonic* and *d-talonic acids* (configurations 7*d* and 5*d* on p. 234) was obtained, and separated by crystallization of the cadmium salts.

Reduction of *d-galactonic lactone* yielded synthetic *d-galactose.*

Starting from *d-gulonic acid*, a similar process led to the synthesis of *l-galactose.*

The syntheses of the galactoses imply the synthetic production of *i-dulcitol* and of *i-mucic acid.*

(ii) *d-* (or *l-*) *Talose.* Reduction of the talonic acids obtained together with the galactonic acids in the transference from the pentose *d-* (or *l-*) *lyxose* to the hexoses has furnished the synthetic *taloses* (configurations 5*d* and 5*l*, p. 234).

(iii) *d-* (or *l-*) *Idose.* When *d-* (or *l-*) *gulonic acid* is subjected to intramolecular rearrangement by quinoline, the isomeride produced is *d-* (or *l-*) *idonic acid.* Reduction of the lactone of the latter acid (when purified) yields *d-* (or *l-*) *idose* (configurations 8*d* and 8*l*, p. 235).

These results are summarized in tabular form below:

```
                          α-ACROSE
                             ↓
                     (d- + l-) Mannitol
                             ↓
                  (d- + l-) Mannonic acid

            d-Mannonic acid  ←-→  l-Mannonic acid
                 ↓ ↑                    ↓ ↑
            d-Gluconic acid ←---    l-Gluconic acid ←
                 ↓                      ↓
            d-Saccharic acid ---    l-Saccharic acid —
d-Idonic   →d-Gulonic acid  ←--     l-Gulonic acid  ←   l-Idonic
   |  acid ←     |                      |          --→     |  acid
   ↓             ↓                      ↓          ←--     ↓
d-IDOSE     d-Xylose                l-Xylose            l-IDOSE
                 ↓                      ↓
            d-Xylonic acid          l-Xylonic acid
                 ↓ ↑                    ↓ ↑
            l-Lyxonic acid          d-Lyxonic acid
                 ↓                      ↓
            l-Lyxose                d-Lyxose ———
l-Talonic acid ←—|—→ l-Galactonic acid      |
   |                  |  d-Galactonic acid ←—|—→ d-Talonic
   ↓                  ↓          ↓                  ↓  acid
l-TALOSE        l-GALACTOSE  d-GALACTOSE          d-TALOSE
```

III. SYNTHESES OF THE PENTOSES

The four aldopentoses have been synthesized from the hexoses by Wohl's or Ruff's sugar-degradation processes, three of them directly, the other (*ribose*) by intramolecular rearrangement of the *arabonic acid* formed in the synthesis of *arabinose*.

(A direct synthesis of *ribose* would necessitate degradation of the hexoses,

(1d)	(2d)		d-Ribose,
$CH_2(OH)$	$CH_2(OH)$		$CH_2(OH)$
HO.H	HO.H		HO.H
HO.H	HO.H	⟶	HO.H
HO.H	HO.H		HO.H
HO.H	H.OH		CHO
CHO	CHO		

and neither of these particular sugars have thus far been isolated in either *d*- or *l*-form.)

The syntheses may be thus summarized :

(*a*) *Direct.*

d- (or *l*-) Glucose ⟶ *d*- (or *l*-) ARABINOSE.
d- (or *l*-) Gulose ⟶ *d*- (or *l*-) XYLOSE.
d- (or *l*-) Galactose ⟶ *d*- (or *l*-) LYXOSE.

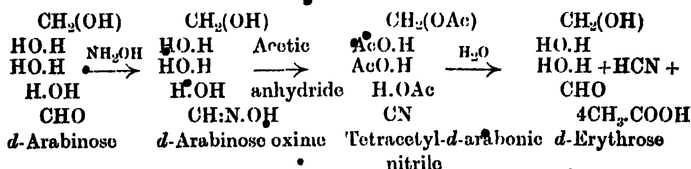
(*b*) *Indirect.*

d- (or *l*-) Glucose→*d*- (or *l*-) Arabonic acid→*d*- (or *l*-) Ribonic acid→*d*- (or *l*-) RIBOSE.
d- (or *l*-) Gulose→*d*- (or *l*-) Xylonic acid →*l*- (or *d*-) Lyxonic acid→*l*- (or *d*-) LYXOSE.

IV. SYNTHESES OF THE TETROSES

d- and *l*-Erythrose, and *l*-threose, have been obtained from *d*- and *l*-arabinose and from *l*-xylose respectively, by means of Wohl's reaction. Since the *arabinoses* and *l-xylose* have been synthesized in the manner indicated in the last section, the tetroses resulting from them by degradation are also completely synthetic products, no new asymmetric carbon atom of undetermined configuration having been added.

The syntheses may be illustrated by that of *d-erythrose* from *d-arabinose* :—



V. SYNTHESES OF THE DIOSES AND TRIOSES

In contrast to the elaborate and connected series of synthetic methods outlined in the preceding sections, and employed in the syntheses of the tetroses, pentoses, and hexoses, those members of the two lowest sugars which have hitherto been produced from their elements in the laboratory have been obtained by means

of a variety of quite independent reactions. Most of these syntheses have already been described in dealing with the individual sugars in question; but it will be well to collect in one place the processes involved.

DIOSE. *Glycolose*, $CH_2(OH).CHO$.

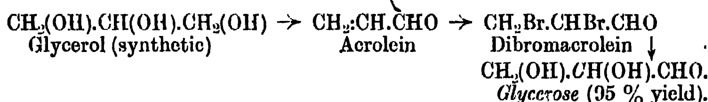
(i) The oxidation of *glycol* is a synthetic method, since the latter compound can be synthesized from *ethylene*.

(ii) Similarly, the preparation of *glycolose* from *monobromacetal* (from acetaldehyde and alcohol) is synthetic.

(iii) Fenton's synthesis from *dioxymaleic acid* (p. 274) is, however, the most complete, since it gives the maximum yield and purest product. The dioxymaleic acid is a synthetic compound, since it is produced from tartaric acid, which has been synthesized in various ways (for example, from *sym*-dibromsuccinic acid, which is produced from succinic acid, obtainable in its turn from the transposition product of potassium cyanide and ethylene dibromide).

TRIOSES. *Glycerose*, $CH_2(OH).CH(OH).CHO$.

The only conclusive synthesis of this sugar is due to Lobry de Bruyn and Adriani, who prepared it from *dibromacrolein* :—

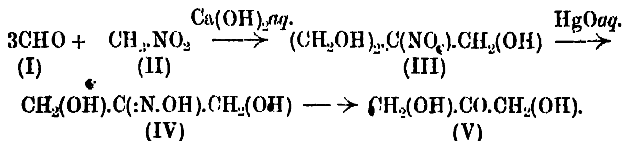


$$\underset{\text{Glycerol (synthetic)}}{CH_2(OH).CH(OH).CH_2(OH)} \rightarrow \underset{\text{Acrolein}}{CH_2{:}CH.CHO} \rightarrow \underset{\text{Dibromacrolein}}{CH_2Br.CHBr.CHO} \downarrow$$

$$\underset{\textit{Glycerose}\ (95\ \%\ \text{yield}).}{CH_2(OH).CH(OH).CHO.}$$

Dioxyacetone, $CH_2(OH).CO.CH_2(OH)$.

This, the lowest member of the ketoses, was synthesized by Piloty from *formaldehyde* (I) and *nitromethane* (II). These condense in presence of aqueous calcium hydroxide to "*nitroisobutylglycerine*" (III), which loses a molecule of formic acid by oxidation in presence of aqueous mercuric oxide, and becomes *dioxyacetoxime* (IV). The action of lime on the latter compound replaces the oximino group by oxygen, thus furnishing *dioxyacetone* (V):



$$\underset{(I)}{3CHO} + \underset{(II)}{CH_3.NO_2} \xrightarrow{Ca(OH)_2aq.} \underset{(III)}{(CH_2OH)_2.C(NO_2).CH_2(OH)} \xrightarrow{HgOaq.}$$

$$\underset{(IV)}{CH_2(OH).C(:N.OH).CH_2(OH)} \longrightarrow \underset{(V)}{CH_2(OH).CO.CH_2(OH).}$$

CHAPTER XVI

THE CARBOHYDRATES: GLUCOSIDES, SYNTHETIC AND NATURAL

THE *monosaccharides*, which form the simplest types of the carbohydrates, have now been reviewed collectively and individually; there remain to be described the various ether-like derivatives of these simpler sugars, which have already been classified (chap. xii. p. 217), but may for the present purpose be rearranged as follows:—

A. GLUCOSIDES.—Ether-like compounds of a monosaccharide with a monohydroxylic compound of more or less simple nature.

(i) *Synthetic*: Compounds with methyl or ethyl alcohol, phenol, etc.

(ii) *Natural*: Substances such as amygdalin, indican, etc.

B. POLYSACCHARIDES.—Ether-like compounds formed from two or more monosaccharides with elimination of water.

(i) *Di- (and tri-) saccharides.* Derived from two (or three) monosaccharide molecules.

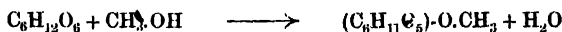
(ii) *Polysaccharides. (The starches and celluloses.)* Derived from an indefinitely large number of monosaccharide molecules.

In this chapter we shall deal with the first of these divisions, namely, the simpler ethereal condensation-products of the monosaccharides, both synthetic and natural.

I. SYNTHETIC GLUCOSIDES

Fischer discovered in 1893 that glucose could be esterified (as it were) by methyl or ethyl alcohol in presence of a small quantity

of anhydrous hydrochloric or sulphuric acid. For instance, methyl alcohol and *d*-glucose reacted to form an ester-like derivative with elimination of a molecular amount of water :



$$C_6H_{12}O_6 + CH_3.OH \longrightarrow (C_6H_{11}O_5)\text{-}O.CH_3 + H_2O$$

The resulting substance was found to be very similar in properties to the glucosides found in many plants, and was named by Fischer *methyl-glucoside*.

We will use the derivatives thus obtained by Fischer from *methyl alcohol* and *d-glucose* as typical illustrations of the compounds which have come to be known as the "synthetic glucosides."

In 1895, Fischer published details of a method which gave him much better yields of "methyl-glucoside" than previously, and he was thereby enabled to show that the product was not homogeneous, but consisted of two isomeric compounds which he termed respectively *α*- and *β-methyl-d-glucoside*.

He heated pure *d*-glucose with the purest obtainable methyl alcohol in presence of 0·25 per cent. of anhydrous hydrogen chloride for an hour under a reflux condenser. On cooling, a 45 per cent. yield of *α-methyl-d-glucoside* separated out, and the filtrates from this were again heated with more of the methyl-alcoholic hydrogen chloride for a day. In this way a further 35 per cent. yield of the *α*-compound was produced, whilst the mother-liquors were found to contain a small amount of the isomeric *β-methyl-d-glucoside*, which is more readily soluble and also melts at a much lower temperature than the former derivative.

By this process Fischer succeeded in converting 100 parts of *d-glucose* to 80 parts of *α-methyl-d-glucoside* and 10 parts of *β-methyl-d-glucoside*. He also found that, instead of *d*-glucose, polysaccharides such as starch, cane-sugar, maltose, etc. (which yield *d*-glucose by hydrolysis) could equally well be employed.

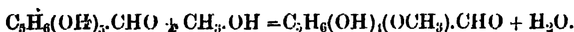
It was observed later that the *β-derivative* passes into the *α-derivative* in presence of alcoholic hydrogen chloride, an equilibrium mixture being set up between the two isomerides which, even at ordinary temperatures, is largely composed of the *α*-form.

Another method of preparation of the compounds, which leads to the production of either form as desired, was worked out somewhat later (about 1900) by Fischer and E. F. Armstrong, and also by Königs and Knorr.

The first pair of chemists showed that by the action of acetyl chloride (or bromide) on *d*-glucose pentacetate, compounds known as *aceto-chloro-* (or *-bromo-*)*-d-glucose* were produced. Now the pentacetates corresponding to the α-, β-, and γ-forms of *d*-glucose (chap. xiv. p. 250) had each been isolated, and it was found that each of the first two of these varieties of *d*-glucose gave rise to a corresponding *α-* or *β-acetochloro-d-glucose.* Then Königs and Knorr proved that, by allowing either form of the *acetochloro*-compounds to stand covered with anhydrous methyl alcohol for some time, the corresponding *α-* or *β-methyl-d-glucoside tetracetates*[1] resulted in excellent yield, and from these by hydrolysis the individual α- or β-varieties themselves followed.

Turning now to the constitution of the *methyl-d-glucosides,* we may observe in the first place that, like similar derivatives from other hexoses or from the aldopentoses, these compounds are well-crystallized substances which may be recovered in the crystalline state from hot alcohol, water, or acetic acid ; they are optically active, stable towards aqueous alkalies, but are hydrolysed more or less readily to the component sugar and alcohol by aqueous mineral acids.

As regards their structure, the most obvious explanation is that one of the many hydroxyl groups in the *d*-glucose molecule is so influenced by its position in the molecule as to become acidic, so that the formation of these glucosides will be represented as :



$$C_5H_6(OH)_5.CHO + CH_3.OH = C_5H_6(OH)_4(OCH_3).CHO + H_2O.$$

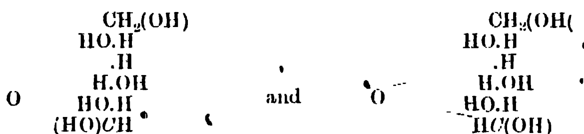
This view is at once invalidated by the following facts :

(i) The *methylglucosides* possess no properties characteristic of the aldehyde group.

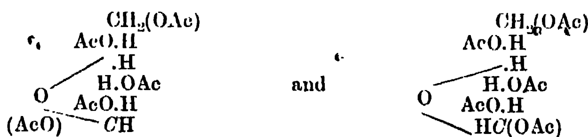
(ii) The relations between the *acetochloroglucoses* (whose structure is known by their relations to α- and β-*d*-glucose) and the *methylglucosides* cannot thus be accounted for.

The first objection suggests that it is the aldehydic group which has been in some way "esterified," and this is borne out by the evidence of the *acetochloro*-compounds, which proves directly the structure of the α- and β-*methylglucosides*, and shows them to be stereochemical isomerides of the type which has become so familiar in the preceding pages.

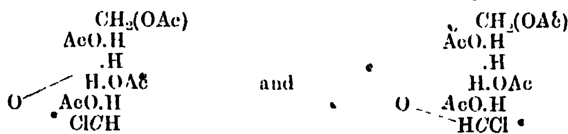
We have seen (chap. xiv. p. 258) that α- and β-glucose are to be represented as:



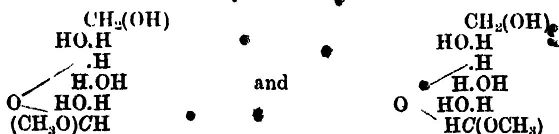
so that (representing the group $-CO.CH_3$ by Ac-) their pentacetyl derivatives are:



The *acetochloro*-compounds are believed to correspond in the following manner:—



Hence, finally, the α- and β-*methyl-d-glucosides* come to be represented as:



The chief synthetic glucosides are enumerated in the following table, and attention is there drawn to their behaviour with the enzymes *zymase* and *emulsin*. In certain cases, the glucosides are hydrolysed by these unorganized ferments, and it will be noticed that:

(i) The only glucosides attacked are those containing the asymmetric configuration common to *d*-glucose and *d*-galactose.

(ii) The *α*-glucosides are attacked by *zymase*, not by *emulsin*; whilst the *β*-compounds are hydrolysed by *emulsin*, but not by *zymase*. (In certain cases only one isomer of the glucosides is known, and it is uncertain with which form (*α*- or *β*-) these should be classed).

Pentosides.	*M.p.*	$[\alpha]_D$	*Action of zymase.*	*Action of emulsin.*
α-Methyl-*l*-Xyloside	92°	+153°	None	None
β- „ -*l*- „	156°	− 66°	None	None
Methyl-*l*-arabinoside	176°	?	None	None
Methylrhamnoside	109°	−62°	None	None
Glucosides.				
α-Methyl-*d*-glucoside	166°	+158°	Hydrolysed	None
β- „ -*d*- „	110°	−32°	None	Hydrolysed
α- „ -*l*- „	166°	−157°	None	None
β- „ -*l*- „	110°	+37°	None	None
α-Ethyl-*d*-glucoside	114°	+151°	Slow hydrolysis	None
β- „ -*d*- „	Syrup	− 30°	None	Hydrolysed
Methyl-*d*-mannoside	191°	+82°	None	Slight hydrolysis
α-Methyl-*d*-galactoside	110°	+179°	None	None
β- „ -*d*- „	176°	+3°	None	Hydrolysed
α-Ethyl-*d*-galactoside	136°	+179°	None	None
β- „ -*d*- „	155°	− 4°	None	Hydrolysed

Some of the related *acetochloro-monosaccharides* are given in the next table.

	α-Variety.		*β-Variety.*	
	M.p.	$[\alpha]_D$	*M.p.*	$[\alpha]_D$
Acetochloro-*l*-arabinose.		—	152°	−225°
Acetochloro-*d*-glucose.	64°	+147°	74°	+166°
Acetochloro-*d*-galactose.		—	82°	+212°

II. Natural Glucosides

The numerous ethereal compounds of glucose which are found in nature are probably constituted very similarly to the synthetic derivatives which have been discussed above, but the substances which have suffered condensation with glucose in the tissues of plants are usually more complicated than those in the synthetic glucosides (*i.e.* methyl or ethyl alcohols, hydrogen chloride, or hydrogen bromide). Several different types of organic compounds (mostly of the aromatic series) are found, in fact, combined with the sugar molecule, notably *aldehydes*, *phenols*, and *esters*.

On the other hand, sugars other than *d-glucose* are occasionally met with in natural glucosides; the chief of these is *d-rhamnose*, the methyl-pentose described on p. 251. Derivatives of *rhamnose* are often termed "pentosides" in distinction to the "glucosides," but, since most frequently those substances which contain rhamnose contain also a molecule of *d*-glucose, this seems an unnecessary distinction, and it is better to refer to the whole class as *glucosides*, defining the latter term as *substances containing organic compounds of various types united in the form of a condensation product with d-glucose, rhamnose, or other monosaccharides.*

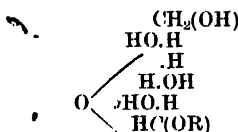
Similarly, the glucosides are often subdivided according to the number of molecules of monosaccharide which they furnish upon hydrolysis; this again is too artificial a method to be of much service, and it is more profitable to group them according to the nature of their non-carbohydrate products.

As a class, the glucosides are solids, usually crystalline, but occasionally amorphous. They possess optical activity as a general rule, and are fairly stable except in presence of hydrolytic reagents.

Their susceptibility to hydrolysis varies greatly; some (but not most) glucosides are decomposed by boiling water or by dilute alkalies; the majority, however, are readily broken up only by the application of aqueous hydrochloric or sulphuric acids. The natural glucosides, like the synthetic compounds, are also hydrolysed by certain enzymes; very frequently an

enzyme which is especially adapted to the hydrolysis of a given glucoside exists in the plant in which the latter occurs.

As regards the constitution of the natural glucosides, it will be inferred that the most favoured view is that the non-carbohydrate constituent (which may be represented as R.OH) is united to the sugar molecule, as is methyl alcohol in the methylglucosides; that is, the glucosides of *d*-glucose may be represented as:



Moreover, there is reason to believe that the more common glucosides, at any rate, are to be considered as *β-glucosides*, in view of the following facts :—

(i) Like the synthetic *β-d-glucosides*, most of the naturally occurring members are hydrolysed by the enzyme *emulsin*, but not (except in rare instances) by *zymase*.

(ii) The few naturally occurring glucosides which have also been synthesized in the laboratory belong to the *β*-type.

Thus *helicin* (*salicylaldehyde-d-glucoside*, which results by oxidation of the natural product *salicin*, showing incidentally that the latter is a condensation product of *salicyl alcohol* and *d-glucose*, and that the condensation must take place through the phenolic hydroxyl radicle of salicyl alcohol) has been synthesized by condensation of *β-acetochloro-d-glucose* (p. 299) with *salicylic aldehyde*, and careful hydrolysis of the resulting *helicin tetracetate*.

The properties of a few of the more important *natural glucosides* are enumerated in the following table (the numbers indicate the molecular proportions of the monosaccharide and the non-carbohydrate products of hydrolysis).

		M.p. $[\alpha]_D$	Products of hydrolysis. Monosaccharide.	Products of hydrolysis. Non-carbohydrate.	Enzyme causing hydrolysis.	Remarks.
Indican (p. 55)	$C_{14}H_{17}O_6N$	Syrup Lævo-rotatory.	1 *d*-Glucose	1 Indoxyl (aldehyde).	Indimulsin.	The natural source of indigo-blue.
Amygdalin	$C_{20}H_{27}O_{11}N$	216° – 41°.	2 *d*-Glucose.	1 Benzaldehyde (aldehyde) +1 HCN.	Emulsin, zymase.	In bitter almonds.
Salicin	$C_{13}H_{18}O_7$	188° – 65°.	1 *d*-Glucose.	1 Salicyl alcohol (phenol).	Emulsin ptyalin	In poplars and willows; its benzoyl derivative also occurs in some poplar species and is known as *populin* (m.p. 180°). Oxidation of *salicin* gives *helicin* (m.p. 175°; see above).
Arbutin	$C_{12}H_{16}O_7$	187°.	1 *d*-Glucose.	1 Hydroquinone (phenol).	Emulsin.	In *Arbutus* species.
Ruberythric acid	$C_{26}H_{28}O_{14}$	260°.	2 *d*-Glucose.	1 Alizarin (phenol).	Emulsin.	The former source of the madder dye.
Quercitrin	$C_{21}H_{22}O_{12}$	168°.	1 Rhamnose.	1 Quercitin (phenol).	—	*Quercitin* is the third in order of importance of the natural dyes.
Digitalin	$C_{27}H_{44}O_{13}$	217°.	1 *d*-Glucose. 1 *d*-Galactose.	1 Digitogenin (phenol) $C_{15}H_{24}O_4$.	—	—
Myronic acid	$C_{10}H_{18}O_{10}NS_2K$	127° – 15°.	1 *d*-Glucose.	1 Allyl isothiocyanate (ester) +1 $KHSO_4$.	Myrosin, emulsin.	—
Phloridzin	$C_{21}H_{24}O_{10}$	158° – 49°.	1 *d*-Glucose.	1 Phloretin (phenol ester).	—	*Phloretin* is *phloglucinol phloretate.*
Naringin	$C_{21}H_{26}O_{11}$	170° – 84°.	1 *d*-Glucose. 1 Rhamnose.	1 Naringenin (phenol ester).	—	*Naringenin* is *phloroglucinol p-oxycinnamate.*
Hesperidin	$C_{22}H_{26}O_{12}$	251° – 89°.	1 *d*-Glucose. 1 Rhamnose.	1 Hesperetin (phenol ester).	—	*Hesperetin* is *phloroglucinol isoferulate.*

CHAPTER XVII

THE CARBOHYDRATES: DI-, TRI-, AND POLY-SACCHARIDES

I. The Disaccharides

THE *disaccharides*, of which we shall especially notice only *arabiose*, *cane-sugar*, *lactose*, *melibiose*, and *maltose*, are composed of two molecules of a monosaccharide (with the elimination between these of a molecule of water).

The most important and abundant of all the natural sugars, *cane-sugar*, is a disaccharide which when hydrolysed yields a molecule each of *d-glucose* and *d-fructose*. In spite of this, it is quite unnecessary to devote any considerable space to the description of this substance and its congeners, for chemically speaking their only characteristic property is their hydrolysis, and their chemical behaviour is summed up in those of their hydrolytic fission products.

Nevertheless, we may glance at the general question of the structure of the disaccharides. The products of hydrolysis of the compounds which we shall mention are as follows :—

Arabiose	yields	*l*-arabinose + *l*-arabinose.
Cane-sugar	„	*d*-glucose + *d*-fructose.
Lactose	„	*d*-glucose + *d*-galactose.
Melibiose	„	*d*-glucose + *d*-galactose.
Maltose	„	*d*-glucose + *d*-glucose.

From these facts it is plain that *arabiose* and *maltose* are more or less similarly constituted, being formed from two molecules of the same aldopentose or aldohexose, and also that *lactose* and *melibiose* are stereoisomeric forms of one and the same disaccharide.

Again, it is found that, of these sugars, *cane-sugar* does not reduce Fehling's solution until after it is hydrolysed, whereas *arabiose*, *lactose*, *melibiose*, and *maltose* reduce it immediately. Similarly, *cane-sugar* does not exhibit polarimetric mutarotation, whilst the specific rotation of the others alters in each case until a constant value is finally attained (as with *d*-glucose, p. 256).

Moreover, *cane-sugar* does not react with phenylhydrazine, although the others form *monophenylhydrazones* and *mono-osazones* just like the monosaccharides.

All these facts point to the existence in the disaccharides other than *cane-sugar* of a free *aldehyde* group, whilst in *cane-sugar* the carbonylic radicles of both *d*-glucose and *d*-fructose have disappeared.

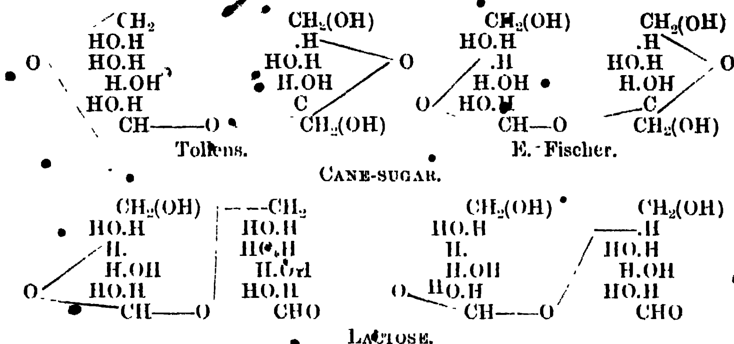
In other words, in the case of cane-sugar, the union of the two constituent monosaccharides is effected by condensation of the hydroxylic forms of the carbonyl group in each monosaccharide; but in the other disaccharides, the condensation must have taken place between the (hydroxylic) aldehyde group of one sugar and an alcoholic hydroxyl radicle from the other.

Finally, all the hexose disaccharides yield *octacetyl*-derivatives, so that they must be formulated as $C_{12}H_{14}O_3(OH)_8$. Of the remaining oxygen atoms, one is utilized in forming the ethereal link between the constituent monoses; the other two must be supposed to occur in internal anhydride or lactide-like formations.

It is nevertheless impossible from the above data to define a stereochemical formula for each of the disaccharides, since there is a super-abundance of free hydroxyl groups which may enter into the ethereal or anhydride-like structures.

Based on various (usually involved) specific reactions of each sugar, different constitutional formulæ have from time to time been put forward for the above disaccharides. Many of these, however, are conflicting, and it is still uncertain as to which of the numerous guesses is likely finally to prove correct.

We may give two formulæ each for *cane-sugar* and for *lactose*, proposed by Tollens and by Emil Fischer, two of the foremost authorities on the carbohydrates:



Many attempts have been made to synthesize one or other of the disaccharides by condensation of various derivatives of the two monosaccharides concerned. Nearly all of these have proved quite fruitless, except in the case of two, cane-sugar and melibiose (and it is not certain even in these cases that the resulting sugar is completely identical in all respects with the natural compound):

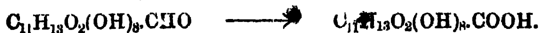
(i) Marchlewski (1899) submitted *potassium d-fructosate* (a compound analogous to those of glucose with baryta or lime, etc.) to the action of an alcoholic solution of *acetochloro-d-glucose* (p. 299) and obtained a mixture of disaccharides which was believed to contain *cane-sugar*.

(ii) Fischer and Armstrong (1901) similarly obtained *melibiose* from *d-glucose* and *β-acetochloro-d-galactose*.

The hydrolysis of the disaccharides, which is best effected chemically by heating with dilute sulphuric acid, is also caused by numerous enzymes, some of which go further and decompose certain of the resulting monosaccharides into alcohol and carbon dioxide (or other products), whilst others only promote the hydrolytic change.

Emulsin, *diastase*, and *zymase* belong to the first class, whilst *invertase* (in yeast), *ptyalin* (in saliva), and *pepsin* (pancreas) belong to the purely hydrolytic enzymes.

The disaccharides which contain a free aldehyde group can be oxidized by chlorine water to corresponding monocarboxylic acids:



$$C_{11}H_{13}O_2(OH)_8.CHO \longrightarrow C_{11}H_{13}O_2(OH)_8.COOH.$$

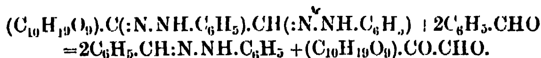
These are termed *bionic acids*, and, when heated with dilute sulphuric acid, they yield a mixture of a monosaccharide and a monosaccharide monocarboxylic acid.

For example, *maltose* oxidizes to *maltobionic acid*, which can be hydrolysed to *d-glucose* and *d-gluconic acid*; *lactose* and *melibiose* give rise respectively to *lactobionic* and *melibionic acids*, both of which yield *d-gluconic acid* and *d-galactose* upon hydrolysis, showing that in each of these sugars it is the *d*-glucose half of the molecule which contains the aldehydic residue.

The following table gives the chief characteristics of the disaccharides:

		M.p.	$[a]_D$	*Octacetate. M.p.*	*Osazone. M.p.*
Arabiose	$C_{10}H_{18}O_9$	Amorphous	+200°	—	—
Cane-sugar	$C_{12}H_{22}O_{11}$	160°	+66°·5	67°	
Maltose	$C_{12}H_{22}O_{11},H_2O$	Amorphous	+137°	156°	206°
Lactose	$C_{12}H_{22}O_{11},H_2O$	205°	+92° to +52°	106°	200°
Melibiose	$C_{12}H_{22}O_{11}$	Amorphous	+100° to +143°	171°	179°

The *osazones* of the *bioses* interact with benzaldehyde, so that benzaldehyde phenylhydrazone is formed, together with the corresponding *osone*:



$$(C_{10}H_{19}O_9).C(:N.NH.C_6H_5).CH(:N.NH.C_6H_5) + 2C_6H_5.CHO$$
$$= 2C_6H_5.CH:N.NH.C_6H_5 + (C_{10}H_{19}O_9).CO.CHO.$$

Cane-sugar (or *saccharose*) occurs abundantly in the American sugar-cane, in the sap of many other trees, and also in many vegetables, notably the sugar-beet, in which it was first found by Marggraf in 1747. At the present time the beet-sugar industry competes successfully with the older cane-sugar plantation method. It is carried on mainly on the Continent, although the sugar-beet is beginning to be cultivated now in England.

Cane-sugar is of prime importance for the alcohol and spirit industry, in addition to finding enormous use as a sweetening principle in culinary operations. The details of its purification for the latter purpose, and of its conversion by fermentation to spirit of various kinds, are given in elementary and other text-books, and do not concern us so much here as does its chemical behaviour, which will accordingly receive the greater share of attention.

When *cane-sugar* is hydrolysed, the specific rotatory power

changes from $[\alpha]_D = +66 \cdot 5°$ to the mean of those of *d*-glucose ($+52 \cdot 5°$) and *d*-fructose ($-93°$), *i.e.* $[\alpha]_D = -21°$.

The resulting equimolecular mixture of *d-glucose* and *d-fructose* is called "*invert-sugar*," owing originally to the fact that the sign of the rotatory power has changed.

It may be noticed in passing that *invert-sugar* frequently accompanies *cane-sugar* in nature in many fruit-juices, especially in the over-ripe condition.

This change in rotation on hydrolysis (or *inversion*, as it is usually termed in the case of cane-sugar) can be applied to the estimation of *cane-sugar*, either alone or in the presence of other sugars whose rotatory powers remain constant (*i.e.* of monosaccharides).

The rate of hydrolysis of sugar solutions has served as a favourite theme for researches bearing on the law of mass-action, or upon the relative effects of different acids in promoting hydrolysis (Wilhelmy, Ostwald, etc.).

Maltose (or *malt-sugar*) does not occur as such in nature, but is obtained in the fermentation of starch by malt.

Lactose (or *milk-sugar*), on the other hand, is found in the milk of nearly all mammals, but does not occur to any extent in the vegetable kingdom. It is one of the oldest known sugars, attention having been called to it as early as 1615.

Finally, *melibiose* is an artificial disaccharide, in so far as it is a partially hydrolysed form of the naturally occurring trisaccharide *raffinose*; and *arabiose*, the pentose disaccharide, like its hexose analogue *maltose* (*cf.* p. 311), is found as a fermentation product or acid hydrolysis product of *arabinic acid*, a polysaccharide or starch of the pentose series (p. 312).

II. The Trisaccharides

The most important trisaccharide is *raffinose*, a sugar occurring in cotton-seed flour and in certain varieties of manna; it possesses the formula $C_{18}H_{32}O_{16}$, and upon hydrolysis yields *d-fructose*

and *melibiose*, the latter by prolonged hydrolytic action decomposing into *d-glucose* and *d-galactose*, as already shown.

Raffinose crystallizes with five molecules of water of crystallization, and in aqueous solution has $[\alpha]_D = +105°$. It does not form phenylhydrazone, but yields a *dodecacetate*, $C_{18}H_{20}O_4.(O.CO.CH_3)_{12}$, which is a low melting solid of $[\alpha]_D = +100°$.

Rhamninose, $C_{18}H_{32}O_{14}$, is a pentose trisaccharide, found in the glucoside *xanthorhamnin*, which melts at 140° and has the specific rotatory power $[\alpha]_D = -41°$. On hydrolysis it gives one molecule of *d-glucose* and two molecules of *rhamnose*. It is not easily attacked by ferments; it forms an *octacetate*, m.p. 95°, and a very soluble *osazone*.

By gentle oxidation it forms *rhamninotrionic acid*, $C_{18}H_{32}O_{15}$, which is of interest because it is a *trisaccharide monobasic acid* exactly corresponding to the disaccharide monobasic lactobionic or maltobionic acids, or the monosaccharide monobasic acids such as *d*-gluconic acid.

III. The Polysaccharides

The *polysaccharides* are not so closely connected with the lower saccharides as the latter are with each other. They are colloidal compounds of great molecular weight, belonging to both the pentose and hexose series. Nothing is known of their internal structure, and the difficulty of unravelling even the outlines of their structure is increased by the fact that all of them, pentose derivatives as well as hexose derivatives, possess the empirical formula $C_6H_{10}O_5$.

On boiling with water or dilute acids, the polysaccharides break down into monosaccharides, and as a general rule only one simple sugar is produced by the hydrolysis of any given polysaccharide.

We must restrict our attention, then, to the classification of the polysaccharides by means of their decomposition products, and it may be noticed that the most prominent workers in this field have so far been Tollens, O'Sullivan, and especially Cross and Bevan.

There are three main classes of polysaccharides—*starches*, *gums*, and *celluloses*.

The *starches* occur in vegetable and animal cells in great quantity. The various starches which can be distinguished individually do not, however, possess all the characteristics of a true homogeneous compound. Thus most starches are partly soluble in and partly insoluble in water, and it is not definitely known whether these two parts represent distinct chemical individuals or whether the soluble (*granulose*) and insoluble (*starch cellulose*) portions correspond simply to the soluble (*hydrosol*) and insoluble (*hydrogel*) forms of the same colloid.

The molecular magnitude of the starches is also uncertain, but it is probably well over 30,000.

Both the granuloses and starch celluloses form characteristic dark blue colouring matters with iodine.

Most starches are fermentable by varieties of the enzyme *diastase* to disaccharides, amongst which *maltose* occurs most frequently.

On the other hand, prolonged heating with water produces first a *gum*, and then this substance is further hydrolysed to monosaccharides.

The *gums*, besides being intermediate products in starch hydrolysis, occur in nature themselves, chiefly in the vegetable kingdom, either in the plant-sap, or in the form of exudations on the surface of the stem, leaves, or flowers.

The gums are colloidal compounds which dissolve easily in water, but are insoluble in alcohol. They are fermentable by diastase, but not by zymase, invertase, or emulsin. Like the starches, they show optical activity, but presumably contain no free aldehydic group, since they exert no reducing action on ammoniacal silver or copper solutions.

The *celluloses* are slightly more definite in character, and yield various derivatives of a more or less workable character. They occur in nature as the chief constituents of the walls of the plant cells, and are amorphous, but not so gelatinous as the starches or gums.

They yield *hexacetyl* derivatives, so that their molecular formula must be a multiple of at least $C_{12}H_{20}O_{10}$ rather than $C_6H_{10}O_5$.

The *hexacetates* are thus $C_{12}H_{14}O_4(O.CO.CH_3)_6$.

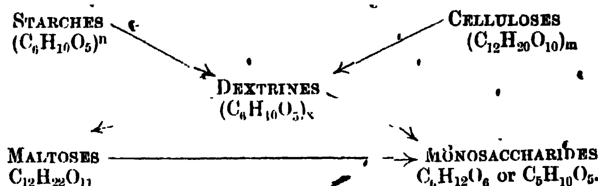
The esters of cellulose and nitric acid are very important technically.

Gun-cotton is essentially *cellulose hexanitrate*, $C_{12}H_{14}O_4(O.NO_2)_6$, and this, when fused with camphor, yields the inflammable and exceedingly dangerous horn substitute termed *celluloid*.

Collodion is a solution of *cellulose tetranitrate*, $C_{12}H_{16}O_6(O.NO_2)_4$, in ether-alcohol, and finds application in the covering of photographic films.

The celluloses are not so readily hydrolysed as the starches, but, like the latter, ultimately break down into dextrine, and then into monosaccharides.

We may therefore depict the relations of the polysaccharides to the monosaccharides somewhat as follows :—



We may illustrate the further detailed classification of the polysaccharides by quoting a very few of the best-known individual members.

POLYSACCHARIDES

A. Pentose Derivatives

I. Starches.	Not well known.	
II. Celluloses (Furoids).		*Derived from*
Cereal-celluloses	In cereals.	Arabinose and xylose.
Ligno-celluloses.	In wood-fibre.	Arabinose and xylose.
III. Gums (Pentosanes).		
Pectinic (Arabinic) acid.	Apple and cherry-juice.	*l*-Arabinose.
Beechwood gum.	Beeches.	*l*-Xylose.
Cherry-gum.	Cherry-trees.	*l*-Arabinose.

B. Hexose Derivatives

I. Starches.		
Starch.	Most plant-cells.	*d*-Glucose.
Glycogen	Most animal-cells.	*d*-Glucose.
Lichenin.	Mosses and lichens.	*d*-Glucose.
Inulin.	Dahlia, potatoes, and many *Solanaceæ* and *Compositæ*.	*d*-Fructose.
Mannin.	Yeast.	*d*-Mannose.

II. Gums (Glucosanes).

Dextrine.	Many plants, glue, etc.	*d*-Glucose.
Gum arabic.	Various plants.	*d*-Galactose.
Mannanes.	Yeast, sunflowers, dandelions, chicory, etc.	*d*-Mannose.
Galactanes.	Lucern, lupins, and other *Leguminosæ.*	*d*-Galactose.
Fructosanes.	Sugar-beet, etc.	*d*-Fructose.

Many gums have been found to give mixtures of two or more monosaccharides on hydrolysis, and are therefore classed as, for example, *glucomannanes, galactomannanes, mannofructosanes,* etc., etc.

III. Celluloses.

Glucocelluloses. *Mannocelluloses.* *Fructocelluloses,* etc., etc.	Plant and wood fibre.	*d*-Glucose. *d*-Mannose. *d*-Fructose, etc., etc.

CHAPTER XVIII

THE TERPENES: GENERAL CLASSIFICATION AND CHARACTERISTICS

THE latter half of the present book gives some account of various classes of organic compounds met with in the vegetable and animal kingdoms; we have in turn reviewed:

(i) The *alkaloids* found in plant juices, and derived for the most part from heterocyclic nitrogen bases.

(ii) The purines, or *uric acid series*, which occur both in plants and in animal tissues, and contain the heterocyclic pyrimidine nucleus (or may be viewed alternatively as condensation products of urea).

(iii) The *proteins*, which are mainly animal products, and are complex condensed aliphatic aminoacids.

(iv) The *sugars* and *starches*, found in both animal and vegetable realms, and composed of polyhydric alcohol-aldehydes and -ketones.

This series of naturally occurring substances remains to be completed by a description of the important class of *hydro-aromatic compounds* known as the terpenes.

The generic name of these bodies is due to the fact that the oils from most of the pines and firs (*Coniferæ*) are largely made up of mixtures (turpentine) of various hydroaromatic hydrocarbons of the formula $C_{10}H_{16}$.

Many other plants, however, contain notable quantities either of these hydrocarbons as such, or of their oxygenated derivatives (alcohols, aldehydes, and ketones); this is especially true of the *Citrus* or lemon species, and of the great botanical orders of *Compositæ*, *Labiatæ*, and *Lauraceæ*.

A variety of methods are applied for the technical preparation

from the plants of the "essential oils," as they are termed, which form the concentrated extract of terpenes and other compounds. In some cases, such as that of turpentine, the oil itself is exuded from the bark of the trees containing it, especially upon incision at suitable stages of the growth; generally, however, the plants or shrubs are macerated and then either heated in a current of steam, or pressed by hydraulic or other power, whereby the oils are separated from the cellulose and other constituents of the plant fibre.

Different oils, too, are frequently found concentrated in different parts of a plant; thus *turpentine*, as already stated, is found in the *bark* of pines, firs, larches, etc.; *citral*, the chief constituent of oil of lemon, is derived mainly from the *rind* of the fruit; the essential oils of thyme, lavender, chamomile, and many other *Composites* and *Labiates* occur chiefly in the *leaves* and *stems* of the plants; and *orris oil*, containing the essence of violet perfume, is most profitably obtained from the *rhizome* or tuberous root of the violet plant.

From a chemical standpoint, it is to be observed that most of these naturally occurring compounds are derived from or are themselves hydrocarbons of the composition $C_{10}H_{16}$. Many of them—indeed, practically all the *hydrocarbon* members—are liquids, a smaller proportion (of the oxygenated derivatives) are solids; all the terpenes are characterized by distinct and, as a general rule, pleasant odours, and therefore they find wide application in perfumery of all kinds.

The terpene *hydrocarbons* usually boil at about 160-180° C., and, although hydroaromatic derivatives, are usually not fully hydrogenated. They are thus capable of adding on two monovalent groups; for example, they unite with:

(i) *Bromine* yielding compounds such as $C_{10}H_{16}Br_2$, or $C_{10}H_{16}Br_4$.
(ii) *Hydrogen bromide* ,, ,, ,, $C_{10}H_{16}.HBr$; or $C_{10}H_{16}.2HBr$
(iii) *Nitrosyl chloride* ,, ,, ,, $C_{10}H_{16}.NOCl$.
(iv) *Nitrogen trioxide* ,, ,, ,, $C_{10}H_{16}.N_2O_3$.

In general, too, these hydrocarbons are very readily oxidized, thereby producing a number of very diverse alcohols, ketones,

and more or less complicated acids. Many of the terpenes can be ultimately oxidized to *terephthalic acid*, a reaction which bears out their intimate relation to the benzene series. A still more general reaction which proves the same fact is the transformation of many terpenes, by suitable reagents, to the aromatic hydrocarbons, *p-cymene* and *m-cymene* ($C_{10}H_{14}$), or to the phenols *thymol* and *carvacrol* ($C_{10}H_{13}.OH$, both derived from *p*-cymene).

On the other hand, whilst many terpenes undoubtedly connected directly with the *cymenes* are evidently simply derived from the partially reduced aromatic hydrocarbons, others (equally readily transformed to these aromatic compounds) contain two hydrocarbon rings fused or "annealed" together, in much the same fashion that naphthalene is composed of two annealed benzene nuclei; and, again, another class of terpenes do not possess a cyclic structure at all, although frequently these also may be easily converted to both monocyclic terpenes and to true aromatic compounds.

Moreover, the terpenes derived from the hydrocarbons $C_{10}H_{16}$ are not the only members of the group. Certain related substances of the formula $C_{15}H_{24}$ are also known, and also one or two of the composition $C_{20}H_{32}$, whilst the important class of natural substances known as the *resins* or aromatic gums are related to the "true" terpenes in somewhat analogous fashion to the relation of the starches and celluloses to the sugars (*cf.* chap. xvii. p. 310). In other words, whilst we have the simpler hydrocarbons corresponding to molecular formulæ $(C_5H_8)_2$, $(C_5H_8)_3$ and $(C_5H_8)_4$, the resins are expressed as $(C_5H_8)_x$, their molecular magnitude being unknown, but certainly very great.

All the terpenes may thus be regarded, for purposes of classification, as polymerides of a simple hydrocarbon of the formula C_5H_8. (The hydrocarbon in question is termed *isoprene*, and is dealt with on p. 354.) The usual system of classification of the terpene hydrocarbons is therefore as follows :—

Hemiterpenes, C_5H_8. Not found in nature.

Terpenes $(C_5H_8)_2 = C_{10}H_{16}$. The largest class of natural terpenes.

Subdivided into :

Monocyclic terpenes (containing only one carbon ring).

Dicyclic terpenes (containing two annealed hydrocarbon ring-systems).

Olefinic terpenes (open-chain compounds).

SESQUITERPENES $(C_5H_8)_3 = C_{15}H_{24}$. Less numerous.

DITERPENES $(C_5H_8)_4 = C_{20}H_{32}$. Very little known at present.

POLYTERPENES $(C_5H_8)_x$. Resins and indiarubber.

Many of the transformations of the different monocyclic terpene compounds related to the cymenes are so intricate that it is especially important in this case to have the assistance of a clear and concise system of nomenclature. The generally accepted plan is to consider all these terpenes as unsaturated derivatives of the hexahydrocymenes or *menthanes*, as they have been termed. The specific relationship to *p*- or *m*-cymene is then indicated by the usual prefix (*p*- or *m*-), and the degree of unsaturation (and also, if necessary, any substituent radicle) is denoted in accordance with the "Geneva" nomenclature. Thus we have, for instance :—

$CH_3-CH<(CH_2-CH_2)(CH_2-CH_2)>CH-CH(CH_3)_2$

p-Menthane
(Hexahydro-*p*-cymene)

$CH_3-C<(=CH-CH)(CH_2-CH_2)>C-CH(CH_3)_2$

One of the *p*-Menthadienes

The position of the unsaturated linkings or of substituents is indicated by prefixed numbers referring to the carbon atom of the menthane nucleus in accordance with the following scheme :—

(7) (1) C, (2) C, (3) C, (4) C, (8) C, (9) C, (10) C, (5) C, (6) C

Thus the above unsaturated hydrocarbon is termed $\Delta^{1,8}$-*p*-*menthadiene,* it being generally sufficient to specify only one carbon atom in each double union.

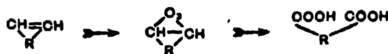
The *constitutions* of the terpenes have received much attention during the past thirty years, the bulk of the work done relating to their decomposition under a most extended variety of conditions. The chief workers from this point of view have been Baeyer, Wallach, Wagner, Semmler, and Tiemann, though numerous other names might well be included here.

We may indicate very cursorily some of the main types of reactions which have been utilized in elucidating the structure of the terpenes.

I. *Oxidation.*

The behaviour of the terpenes to oxidizing agents has probably proved more useful than any other chemical reaction. The chief oxidants employed have been :

(i) *Ozone.* Harries has shown that an ethylenic union absorbs ozone with the formation of "*ozonides*," which on treatment with alkali or other suitable reagent break down into a mixture of acids :



(ii) *Hydrogen dioxide* or ice-cold aqueous 1 per cent. solution of potassium *permanganate* introduces two hydroxyl groups into an ethenoid system :



(iii) More concentrated aqueous potassium permanganate usually ruptures the ethenoid bond and produces a dicarboxylic acid, a ketonic acid, or other products of the same or less carbon content as the original unsaturated subsatnce, according to the nature of the groups adjacent to the double linking.

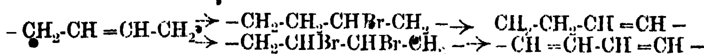
(iv) *Nitric acid* generally (but not by any means invariably) exerts a more disruptive effect than permanganate, and causes a terpene molecule to break down into a number of simpler aliphatic or aromatic acids.

II. *Addition reactions.*

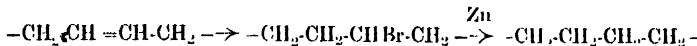
The addition products of unsaturated terpenes with halogens or nitrosyl chloride have frequently proved useful in determining the relationships between the terpenes.

(i) *Halogen addition products.*

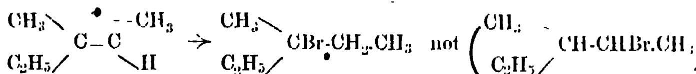
(*a*) The added halogen may sometimes be removed by the action of potash or aromatic bases, such as aniline or quinoline, leading to compounds of different constitutions :—



(*b*) Occasionally the halogen may be removed by treatment with zinc dust and acetic acid, the total effect being to saturate the original ethylenic union :

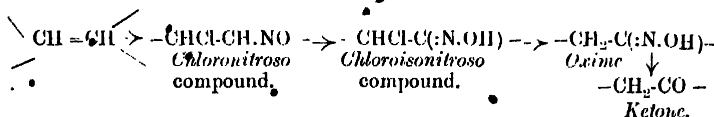


(*c*) In deciding the constitution of a monohalide addition product, the "Markownikow rule" has often proved very useful. This states that in such cases the halogen atom attaches itself to the carbon atom, which is already directly united with fewest hydrogen atoms. Thus—



(ii) *Nitrosyl chloride addition products.*

Nitrosyl chloride unites additively with an ethenoid bond, forming a compound of the formula illustrated below : this compound usually exists, however, not as a *nitroso-*, but as an *isonitroso-*derivative, as shown. By suitable treatment (reduction, or elimination as hydrogen chloride by means of a base), the chlorine atom is removed or replaced by hydrogen, and there remains the *oxime* of a ketone :—



It may be remarked that the oximes of the terpene ketones have been found exceptionally serviceable in constitution-determination, since they are markedly reactive, and undergo numerous transformations, as will appear from the specific examples cited in the following chapters.

III. *Dehydration.*

(i) Many oxygenated cyclic terpenes are rearranged, with loss of one or more molecules of water, to aromatic compounds, by the action of dehydrating agents such as phosphorus pentoxide, potassium hydrogen sulphate, zinc chloride, or glacial acetic acid and sulphuric acid.

(ii) Similarly, the milder of the dehydrating agents mentioned convert some of the oxygenated olefinic or non-cyclic terpenes to derivatives of the monocyclic series.

IV. *Physical characteristics.*

Of late years the advance in our knowledge of the relations between chemical structure and such properties as molecular refractivity, magnetic rotatory power, absorption spectra, and heats of combustion has been so great that these are becoming of frequent assistance as subsidiary aids to chemical proofs of the constitution of the terpenes as well as of many other types of organic compound.

It may also be mentioned here that nearly all the natural terpenes contain asymmetric carbon atoms in their molecules, and so are frequently found to exist in optically active forms. As a general rule, only one form (*dextro-* or *lævo-*rotatory) is found in nature, but there are several exceptions to this, such as *limonene*, $C_{10}H_{16}$ (which occurs in *dextro-*, *lævo-*, and *racemic* varieties, the latter being known as *dipentene*), and *camphor*, which is also found (in different plants) in both optically active forms, as is also its reduction product, the alcohol *borneol.*

Synthetic reactions have also been applied to the terpenes, the first serious efforts being due apparently to Baeyer. Later, Haller, Klages, and Komppa succeeded in synthesizing a few terpene derivatives such as menthone and camphor, but until a few years ago it was difficult synthetically to prepare compounds of the hydroaromatic series containing such a relatively complex group as the *isopropyl* residue present in the cymenes.

Two new reactions, however, have come to light which are of the utmost value in this connexion :—

(i) The direct hydrogenation method of Sabatier and Senderens, whereby an aromatic derivative may be reduced to the hydroaromatic condition by passing its vapour, mixed with hydrogen, over reduced nickel at 250°.

(ii) The synthetic application of the "Grignard reagent" (magnesium alkylhalides, $Mg\begin{matrix} / R \\ \backslash X \end{matrix}$), by means of which alkyl radicles such as *methyl* or *isopropyl* may be introduced at will into practically any compound containing a ketonic, aldehydic, or carboxylic group at a suitable position in the molecule.

The last method is proving exceptionally fruitful in the hands of Prof. W. H. Perkin and his co-workers at the Universities of Manchester and Oxford.

Before commencing the detailed description of the individual classes of terpenes, it may be found instructive to view in tabular form a few of the chief sources of some of the more common hydroaromatic derivatives.

Botanical Family.	*Plant.*	*Hydrocarbons.*	*Alcohols.*	*Aldehydes & Ketones.*	*Non-terpene Compounds.*
CONIFERÆ.	Pines (American, French, and Austrian).	Chiefly *d*- or *l*-Pinene.			
	Russian Pines.	Pinene (and Camphene ?).			
	Distillation of Pine-tar (Turpentine).	Pinene, Sylvestrene, Dipentene, Terpinene.			
	Pine-needles from cones of Pines, Spruces, Larches, etc.	*d*- or *l*-Pinene, *l*-Limonene, *l*-Phellandrene, Dipentene.	*l*-Borneol (as acetate).		
GRAMINEÆ.	Geranium.	Dipentene.	Geraniol.		Hexoic-acid Esters.
	Lemon-grass.		Linalool.	Citral.	Hexoic-acid Esters.
PIPERACEÆ.	Cubebs.	Pinene, Camphene, dipentene, cadinene.			

Botanical Family.	*Plant.*	*Hydrocarbons.*	*Alcohols.*	*Aldehydes & Ketones.*	*Non-terpene Compounds.*
LAURACEÆ.	Camphor-tree.	Pinene, Phellandrene.	Terpineol.	Camphor.	Eugenol (*phenol*).
	Cinnamon.	Phellandrene.		Camphor.	Cinnamic aldehyde.
	Sassafras.	Pinene, myrcene.	Geraniol.	Citral, Camphor.	Safrol (*phenol*).
	Laurel	Pinene.	(Cineol).		Lauric acid.
RUTACEÆ.	Lemon.	*d*-Limonene, Phellandrene.		Citral, Citronellal.	
	Bergamot.	*d*-Limonene.	Linalool (active).		
	Neroli.	*d*-Limonene.	Linalool, Geraniol.		Methyl-anthranilate.
MYRTACEÆ.	Myrtle.	*d*-Pinene, Dipentene.	(Cineol).		
	Bay.	Myrcene, Phellandrene.			Eugenol.
	Cajeput.	*l*-Pinene.	Terpineol (Cineol).		
	Eucalyptus.	*d*- and *l*- Pinene.	(Cineol).	Citral, Citronellal, Menthone.	Cumaric aldehyde.

UMBELLIFERÆ.	Anise.	Pinene.			Anethol (*phenol*).
	Fennel.	Phellandrene.		Fenchone.	Anethol.
	Dill.	Phellandrene, Limonene.		Carvone.	
LABIATÆ.	Rosemary.	Pinene, Camphene.	Borneol (Cineol).	*d*-Camphor.	
	Lavender.		Geraniol, Linalool.		(Acetic acid esters.)
	Spike.	*d*-Camphene.	*d*-Borneol.	*d*-Camphor.	
	Horsemint, Thyme.	*p*-Cymene.			Thymol (*phenol*).
	Peppermint.		*l*-Menthol.	*l*-Menthone.	
	Spearmint.	*l*-Limonene.		*l*-Carvone.	
COMPOSITÆ.	Feverfew.		*l*-Borneol.	*l*-Camphor.	
	Tansy.			*l*-Camphor, Thujone.	
	Wormwood.	Phellandrene, Cadinene.	Thujyl alcohol.	Thujone.	

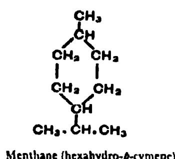
CHAPTER XIX

MONOCYCLIC TERPENES (DERIVED FROM *p*-MENTHANE OR FROM *m*-MENTHANE)

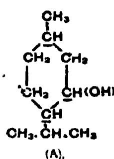
I. Some Saturated Oxyderivatives of *p*-Menthane

THE constitution of the unsaturated hydrocarbons of the *p*-menthane series which form so large a proportion of the naturally occurring turpentine oils and resins has been determined mainly by means of the properties and transpositions of their numerous oxidation products, of which the alcohols and ketones are the simplest and most nearly related compounds to the terpenes themselves; it is therefore well to consider these first.

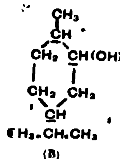
The two simplest of various monohydroxy-*p*-menthanes can be represented as follows:—



Menthane (hexahydro-*p*-cymene)

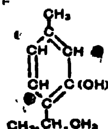


(A).



(B)

Now *l-menthol*, $C_{10}H_{20}O$, which is found plentifully in various species of mint (especially pepper- and horse-mints), has a composition corresponding to that of a *monoxymenthane*, and, moreover, it can be transformed by a series of reactions to *thymol*, the phenol of the composition—

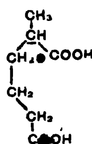


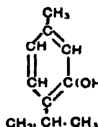
When oxidized by chromic acid, *l*-menthol yields *l-menthone*, which also occurs in the oil from peppermint, and the constitution of which has been definitely shown by the following reactions :—

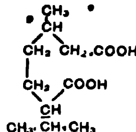
(i) When oxidized by permanganate, *β-methyladipic acid* (I) is produced, and this acid could only result if the methyl- and isopropyl-radicles in menthone were in *para*-positions to each other.

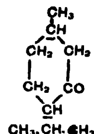
(ii) When brominated in chloroform solution, a *dibrommenthone* is formed, and this upon heating with quinoline loses two molecules of HBr and becomes *thymol* (II).

(iii) *Synthetically*, it was shown in 1905 that distillation of the calcium salt of (synthetic) β-methyl-a^1-isopropylpimelic acid (III.) produced *menthone*, which must therefore receive the formula IV. :









Since menthol is produced by alkaline reduction of menthone, the constitution of menthol must correspond to formula (A) on p. 324, so that the compound is hexahydrothymol.

The isomeric substance of formula (B) is also known, and is called *tetrahydrocarveol* ; it is an oily liquid which we shall meet again later (p. 349) when dealing with the ketone *carvone*. *l-Menthol* is a crystalline solid, melting at 42°, and possessing a very characteristic smell. It forms crystalline esters with numerous organic acids ; we may mention the *benzoate*, m.p. 55°.

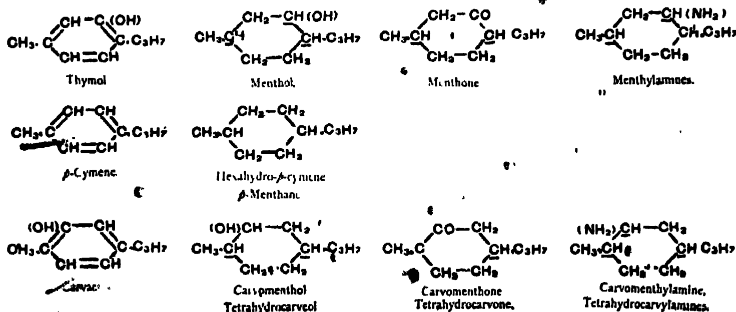
It will be noticed that whilst *menthol* contains three atomic centres of asymmetry, its oxidation product, *menthone*, possesses only two. Consequently, whilst *l*-menthol, $[\alpha]_D = -48°$, when oxidized yields *l*-menthone, $[\alpha]_D = -28°$, the reduction of the latter compound produces two optically isomeric menthols, owing to the production of the *lævo-* and *dextro-* forms of a new "asymmetric carbon atom."

Moreover, the asymmetric atoms in menthol and menthone, as

in many other bodies of the hydroaromatic group, appear to be very labile, so that it is often difficult to preserve the optical homogeneity of these compounds in many of their reactions. Thus the *l*-menthone formed by oxidation of *l*-menthol is completely "inverted" by cold sulphuric acid to *d-menthone*, $[\alpha]_D = +28°$, whilst when phosphorus pentachloride is warmed with *l*-menthol, a mixture of at least three optically isomeric *menthyl chlorides* results.

When the *oxime* of *menthone* is reduced, a mixture of two optically isomeric *menthylamines* is formed. The bases, which can be separated by fractional crystallization of their acyl derivatives, are strongly alkaline liquids.

We have drawn attention to menthol and its nearly allied compounds not so much for their intrinsic importance, as because they form a more self-contained group of derivatives than the majority of the terpene bodies, whilst in our dealings with the latter we shall repeatedly encounter reactions of a precisely similar character to those described in this and the following section, which is given to a description of some monoethylenic derivatives of *p*-menthane. Before proceeding thereto, we will illustrate diagrammatically the connexion between *p*-cymene, the above-mentioned *menthol*-derivatives, and the closely related isomeric series—the *tetrahydrocarveol* type—whose constitutions cannot be explicitly determined without reference to a number of other more complex terpenes (*cf.* pp. 335 *et seq.*):—

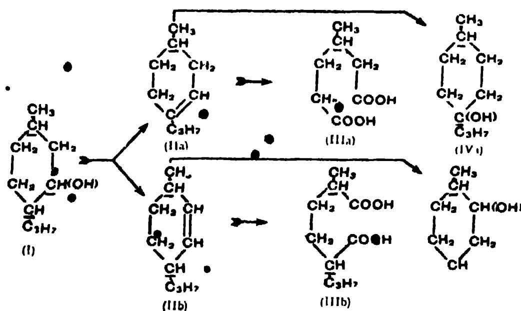


II. Some *p*-Menthene Derivatives

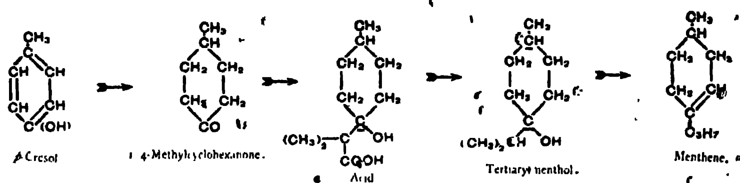
There are a number of possible isomeric forms for the mono-ethenoid hydrocarbons, $C_{10}H_{18}$, corresponding to *p*-menthane; one of these unsaturated hydrocarbons, *menthene*, is formed when menthol is carefully dehydrated. Knowing the constitution of menthol (I), we see that *menthene* may be formulated either as IIa or IIb. We can decide between these formulæ as follows :—

(i) Permanganate oxidation of menthene leads finally to *β-methyladipic acid* (IIIa), so that *menthene* must be IIa, since oxidation of IIb would produce *α*-methyl-*α*[1]-isopropyladipic acid (IIIb).

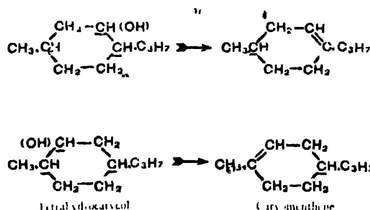
(ii) This structure is confirmed by the reaction of *menthene* with hydriodic acid, when an *iodomenthane* is produced which in presence of silver acetate furnishes an *oxymenthane*, identical neither with *menthol* itself (I) nor with *tetrahydrocarveol* (IVb), which is the only likely alternative from the isomeride IIb. The new alcohol must therefore be represented as IVa, and is known as *tertiary menthol*.



(iii) *Menthene* was synthesized from *p*-cresol by Wallach in 1906; the vapour of *p*-cresol, when reduced by hydrogen in presence of nickel, yields a mixture of 1,4-methylcyclohexanol and 1,4-methylcyclohexanone; the latter substance condenses with ethyl *α*-bromoisobutyrate in presence of zinc dust to the ester of an acid which, by loss of CO_2 on heating becomes *tertiary menthol*; this compound reverts to menthene when heated with sulphuric acid :—



Just as tetrahydrocarveol is a position-isomeride of menthol, so it furnishes by dehydration a *carvomenthene*, which by similar reasoning to that used in the case of menthene is shown to be constituted as follows :--



III. Terpineol and Allied Compounds

We must now pass on to a number of compounds more nearly connected with the hydrocarbon constituents of the turpentine oils, which latter possess in general the composition $C_{10}H_{16}$, corresponding to *menthadienes*, rather than *menthenes*, and thus containing two ethylenic linkings in the hydrocarbon molecule.

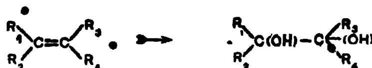
There are two *oxycompounds* upon the constitutions of which, more than of any other terpene derivatives, depend the structural formulæ which are assigned to the *p-menthadienes* (we leave the *m*-menthane derivatives out of consideration for the present); the substances in question are the alcohol *terpineol* and the ketone *carvone*. We shall therefore devote the present section to a brief study of terpineol and other *alcoholic* derivatives of the *p*-menthadienes, whilst the next will be given to a description of carvone and some other *ketonic* compounds of interest in the chemistry of the terpenes.

Terpineol, $C_{10}H_{18}O$, occurs in nature associated with the terpene hydrocarbons, and is also formed when a solid compound termed *terpin hydrate*, $C_{10}H_{20}O_2$, H_2O (which results when turpentine oil is shaken with cold and very dilute aqueous nitric acid), is dehydrated by means of boiling dilute acids; terpineol itself is also produced by shaking pinene or turpentine oil with very dilute sulphuric acid. It is a low-melting solid with a pleasant smell, is optically inactive, and is readily shown to be a mono hydric alcohol.

Its great theoretical importance lies in the fact that a number of the natural terpenes can be obtained from it by simple dehydration under varying conditions. When it is heated with potassium hydrogen sulphate, there results *dipentene* (which, as will be seen later, is closely related to the two *limonenes*); and again, if anhydrous oxalic acid is employed instead of potassium bisulphate, *terpinolene*, another natural *p*-menthadiene, is produced and this can be further isomerized to *terpinene*.

The constitution of terpineol is fixed with certainty by means of its oxidation reactions, but in addition it has recently been obtained synthetically by Prof. W. H. Perkin of Manchester, who has succeeded within the past few years in applying the Grignard reaction to the synthetic production of many natural as well as purely laboratory terpene compounds.

The study of the oxidation of the terpenes will be found much simplified if it is always borne in mind that the first product of oxidation of an ethylenic linking is the result of the attachment of an hydroxyl group to each carbon atom:



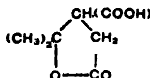
Further oxidation consists of the rupture of the remaining union between what have now become two adjacent alcoholic radicles.

The intermediate *hydroxy-compounds* are frequently non-isolable, but in the case of *terpineol*, when carefully oxidized by dilute permanganate or hydrogen dioxide, the first product, in this case a *trihydroxy-p-menthane*, can be isolated, and is known as *trioxyhexahydro-p-cymene* (V).

Further oxidation of terpineol leads in succession to the following substances :—

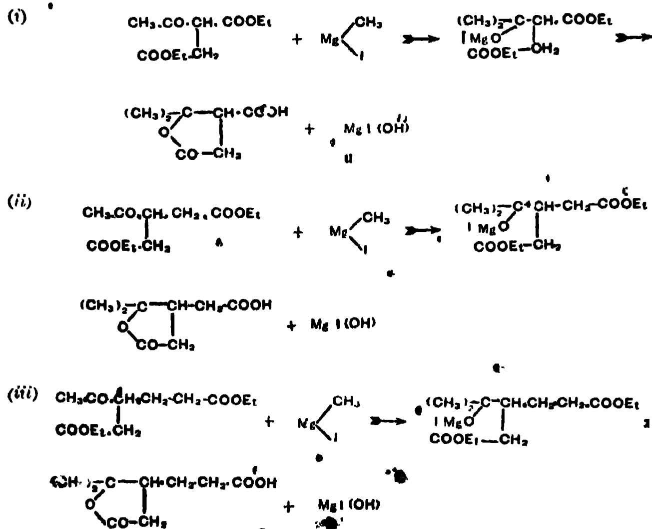
Homoterpenylic methyl ketone, $C_{10}H_{16}O_3$ (IV) ; *terpenylic acid*, $C_8H_{12}O_4$ (II) ; and *terebic acid*, $C_7H_{10}O_4$ (I).

Now we found in chapter iii., p. 31, that *terebic acid* is *dimethyl paraconic acid*, and so possesses the constitution

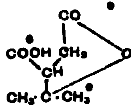


Terebic acid has been synthesized by Fittig in connexion with his work on the paraconic acids (*loc. cit.*), but we may adduce a recent application of the Grignard reaction by Simonsen (1907) to the synthesis, not only of terebic but of terpenylic and homoterpenylic acids.

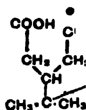
The syntheses consist in the treatment of appropriate *β-acetyl*-esters of the normal succinic-acid series with magnesium methyl iodide; thus we have :—



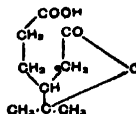
The lactonic acids obtained in the first two cases are respectively identical with the *terebic acid* and *terpenylic acid* formed in the oxidation of terpineol, and we may accordingly reconstruct a formula for terpineol as follows :—



(I) Terebic acid

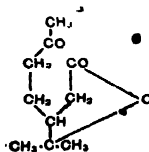


(II) Terpenylic acid

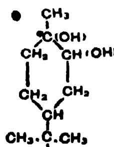


(III) Homoterpenylic acid

The *methyl ketone* of this acid, which results from oxidation of a trioxyhexahydro-*p*-cymene, will therefore be :

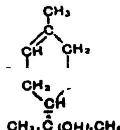


(IV) Homoterpenylic ketone



(V)

Hence it follows that the *trioxy*-compound will most probably have the three hydroxyl groups arranged as in formula (V), and the position of the " double bond " in terpineol is indicated by the position in this formula of the *adjacent* hydroxyl groups, so that terpineol is :



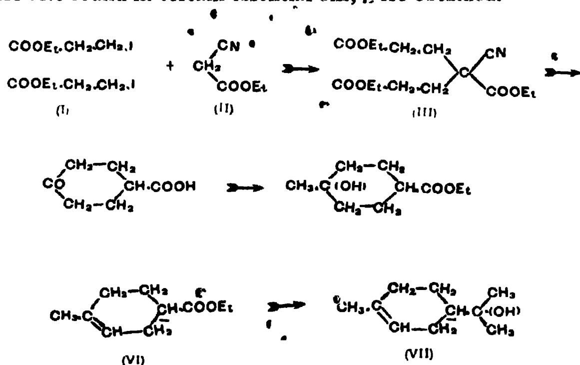
Perkin's synthesis fully confirms this view :

Two molecules of *β-iodopropionic ester* (I) are condensed in presence of sodium ethylate with one molecule of *ethyl cyanacetate* (II), in which the methylic hydrogen groups are replaceable by sodium as readily as those in, for example, diethyl malonate, owing to the influence of the adjacent unsaturated nitrile and carbethoxyl radicles. The condensation product is γ-cyanopentane-*αγε*-tricarboxylic ester (III), which on hydrolysis and

subsequent distillation with acetic anhydride yields, firstly, pentane-$\alpha\gamma\gamma\epsilon$-tetracarboxylic acid, then pentane-$\alpha\gamma\epsilon$-tricarboxylic acid by loss of CO_2, next the anhydride of this acid, and, finally, γ-carboxy-ϵ-ketocyclohexane, more simply termed *δ-ketohexahydrobenzoic acid* (IV).

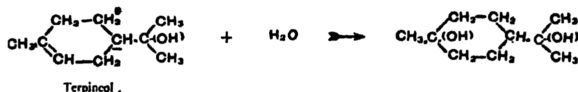
On treatment of the ester of this acid with a molecular proportion of magnesium methyl iodide, the carbonyl group is attacked, and *δ-oxyhexahydro-p-toluic ester* (V) results. Replacement of the hydroxyl group by bromine and elimination of HBr by warming with pyridine leads to the production of *Δ^3-tetrahydro-p-toluic ester* (VI), which by further application of magnesium methyl iodide is transformed to *terpineol* (VII), identical with the natural racemic substance.

Later, the *Δ^3-tetrahydro-p-toluic acid* from (VI), which contains an asymmetric carbon atom in the same position as that present in terpineol, was resolved into its optical antipodes; and when the synthesis of terpineol from the *active* acids was completed, the corresponding *d*- and *l*-terpineols, which are also found in certain essential oils, were obtained.

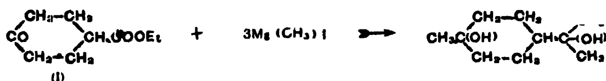


The compound *terpin hydrate*, from which terpineol results on dehydration, can be reproduced from the latter compound by boiling with dilute sulphuric acid. In this reaction two molecules of water are added to one of terpineol, but the product, which is a white crystalline solid melting at 117°, loses one of these when heated at its melting-point for some time. The substance *terpin*, which contains only one molecule of water more than terpineol, is then produced; this is also a solid body, which unites somewhat vigorously with water to re-form the *hydrate*, and which possesses two hydroxylic groups, but is not otherwise unsaturated. Evidently therefore a molecule of water has united with the

" double bond " present in terpineol; and since it is a very general rule that in such addition reactions the non-hydrogen part of the reacting substance becomes united to the carbon atom which is already in union with *least* hydrogen atoms (Markownikow, see p. 319), it is probable that the formation of *terpin* may be thus represented :



This conception is supported by the fact that the same optically inactive terpin is formed from *d*-, *l*-, or racemic terpineol, and by Perkin's synthesis of terpin from *δ-ketohexahydrobenzoic ester* (I), the former terpineol synthesis being modified in that excess of magnesium methyl iodide is allowed to react with that compound, whereby a dihydroxy-derivative (II), identical with *terpin*, is produced :

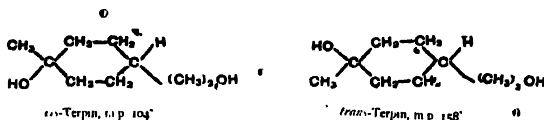


In virtue of its alcoholic nature, *terpin* forms *terpin dibromide* when esterified with hydrobromic acid; this compound is of great importance by reason of its connexion with dipentene and other of the *p*-menthadienes (compare pp. 346, 349).

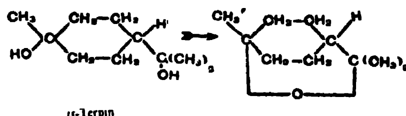
When the *dibromide* is treated with silver acetate, the corresponding *diacetate* is produced, but when this is hydrolysed with alcoholic alkali, a new (stereoisomeric) *terpin* results, which gives a different *dibromide* from that obtained from the original terpin. There is much reason to believe that the isomerism is due to the different arrangement in space of the substituent groups about the central cyclohexane plane, so that it may be explained similarly to that of the reduced benzoic acids (Baeyer), of the fumaric and maleic acid series, or of the *syn*- and *anti*-oximes of Hantzsch.

For several reasons, such as the higher melting-point of the second

mentioned terpin, and of certain chemical reactions of the former terpin, it is supposed that the first named is the *cis*- and the other the *trans*-form :



When the ordinary or *cis-terpin* is boiled with dilute mineral acids a variety of dehydration products result, notably terpineol, dipentene, terpinolene, and a peculiar compound, *cineol*, $C_{10}H_{18}O$, isomeric with terpineol, which is found in many ethereal oils such as those of cajeput, rosemary, and eucalyptus, and which, possessing neither hydroxylic nor ketonic oxygen, would appear to be an internal oxide or ether :



Anhydrous hydrobromic acid converts cineol to *cis*-terpindibromide, as we might anticipate if the annexed formula is correct; whilst, like terpineol and terpin, it can be transformed to *p*-cymene by violent reagents, such as phosphorus halides or pentoxide.

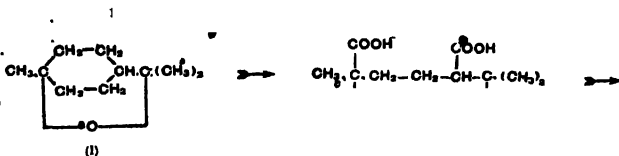
The oxidation of cineol is instructive for two reasons :

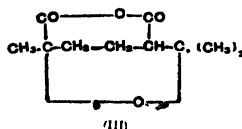
(i) It demonstrates the superior stability of the pentamethylene oxide ring-system compared with that of the cyclohexane nucleus.

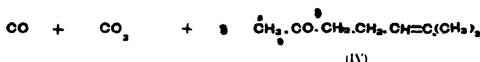
(ii) It affords a connexion between the monocyclic terpenes under discussion and the open-chain olefinic terpenes with which we shall meet in the next chapter.

The action of aqueous potassium permanganate on cineol (I) is to rupture the cyclohexane ring-system and produce the dibasic *cineolic acid* (II); the latter readily yields an *anhydride* (III), which on destructive distillation

furnishes the unsaturated aliphatic ketone, *methyl heptenone* (IV; see p. 356).:







IV. Ketones of the *p*-Menthane Series

There are a number of ketones of the monocyclic terpene series corresponding to *p*-menthane, the *p*-menthenes, and the *p*-menthadienes; the more important of these may be classified with reference to their parent hydrocarbons:

Hydrocarbon.	*Ketones.*
$C_{10}H_{20}$ *p*-Menthane.	$C_{10}H_{18}O$. Menthone, tetrahydrocarvone.
$C_{10}H_{18}$ *p*-Menthenes.	$C_{10}H_{16}O$. Dihydrocarvone, carvenone, carone, thujone, pulegone.
$C_{10}H_{16}$ *p*-Menthadienes.	$C_{10}H_{14}O$. Carvone.

We will deal first with the important compound *carvone*. This occurs as *dextro*-isomer in the oils of dill and of cumin, and as *lævo*-form in spearmint and a few rarer oils. The precise constitution of *carvone* can only be arrived at by a careful consideration of its chemical behaviour under a number of different conditions.

(i) When warmed with dilute aqueous potash, it is rearranged into the isomeric phenolic compound *carvacrol*, $C_{10}H_{14}O$, or

(OH)
C=CH
$CH_3.C$ $C.CH(CH_3)_2$
CH—CH

It is most unlikely that such a relatively mild reagent would cause the migration of oxygen, methyl, or isopropyl from one carbon atom to another, so that we may assume that carvone possesses the skeleton formula:

CO—C   C
C—C   C—C
C—C   C

(ii) Carvone unites with bromine to form the compounds $C_{10}H_{14}OBr_2$ and $C_{10}H_{14}OBr_4$. It thus contains two ethylenic linkings.

(iii) It yields a well-defined *oxime*, the optically active oximes melting at 72°, the racemic form at 93°. On the other hand, it does not react with sodium bisulphite.

(iv) It may be obtained from *terpineol* by a simple series of reactions.

It will be recollected that nitrosyl chloride, NOCl, unites additively with ethylenic substances (I), forming "nitrosochlorides" (II), which, like most nitroso-derivatives, tend to assume the *isonitroso-* or *oxime* form (III):

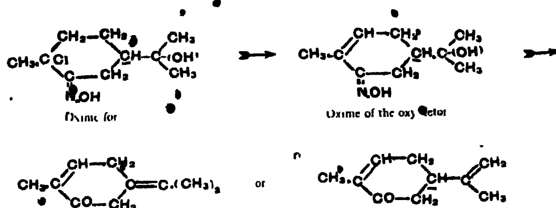
$$\underset{(I)}{R_1CH=CHR_2} \rightarrow \underset{(II)}{R_1CH(NO).CHClR_2} \rightarrow \underset{(III)}{R_1.C(:N.OH).CHClR_2}$$

Now, when *terpineol mononitrosochloride*, $C_{10}H_{16}NOCl$, is treated with alcoholic potash, the oxime, $C_{10}H_{16}O(:N.OH)$, of a ketone is produced; this, by loss of water on heating with dilute mineral acid, becomes *carvone* (the oxime group being simultaneously hydrolysed).

This confirms our supposition that the carbonyl group in *carvone* is adjacent to the methyl-substituted carbon atom, and also fixes the position of one of the double bonds in that ketone, since the series of reactions must be depicted as follows:

$CH_2—CH_2$ CH_3 $CH_2—CH_2$ CH_3
$CH_3.C$ $CH.C(OH)$ → $CH_3.CCl$ $CH.C(OH)$
$CH—CH_2$ CH_3 $CH—CH_2$ CH_3
                         NO

Terpineol.   erpin



(v) Since carvone can possess optical activity, its formula must be the second of the above, there being no asymmetric carbon atom in the alternative one; it is, however, possible that isomerization has accompanied the removal of H_2O in the action of dilute acid, and so more conclusive evidence as to the position of the remaining ethylenic bond would be welcome.

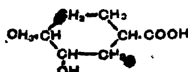
This may be obtained from a study of some reduction products of carvone.

(vi) When carvone is reduced in alkaline media the ketonic group follows the usual custom and becomes transformed to a secondary alcoholic radicle, but in addition one of the ethenoid bonds is reduced, the resulting product, *dihydrocarveol*, $C_{10}H_{18}O$, being still unsaturated but now only capable of uniting with one molecular proportion of bromine or of a halogen acid.

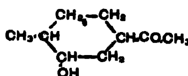
Dihydrocarveol can be oxidized by means of very dilute aqueous potassium permanganate to a *trioxyhexahydro-p-cymene*, $C_{10}H_{20}O_3$ (which is not, however, identical with the compound of similar nature obtained as the first product of the oxidation of terpeneol, p. 329).

One of the three hydroxyl groups present in this compound can be fixed, since it must be the secondary alcoholic radicle originally formed in the reduction of carvone; the positions of the remaining two are at once revealed by further oxidation, which produces a compound containing *two* oxygen atoms, one alcoholic, the other ketonic, and also containing *one carbon atom less* than before. This *ketonic alcohol* has the composition $C_9H_{16}O_2$, and can be further oxidized to an *acid*, $C_8H_{14}O_3$, which gives an *oxy-p-toluic acid*, $C_8H_8O_3$, when heated at 190° with bromine in sealed tubes.

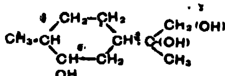
From what we already know of the constitution of *carvone* (compare (i) above), it is evident that the hydroxyl group in the last product of oxidation will be in the *ortho*-position to the methyl radicle, so that the acid, $C_8H_{14}O_3$ (from which the aromatic acid has been produced by removal of six atoms of hydrogen), is:



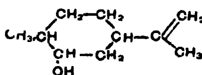
We are now able definitely to fix the position of the second ethenoid bond in *carvone*, for the ketonic alcohol which gives rise to the acid, $C_8H_{14}O_3$, contains one carbon atom more than the latter compound, and is therefore almost certainly



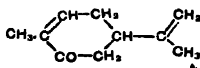
If we refer back, in the next place, to the *trioxyhexahydro-p-cymene*, we find that in turn it possesses one carbon atom more than the ketonic alcohol, $C_9H_{16}O_2$; and, remembering that by its method of formation the presence of two adjacent alcoholic groups is postulated in the trioxy-compound, it is evident that the only possible formula for it which expresses all these facts is:



Accordingly, *dihydrocarveol*, whose oxidation produced the last-named substance, must be



which confirms our original view that *carvone* itself is

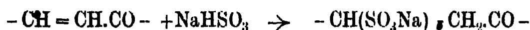


From a theoretical standpoint, it is not without interest that on reduction of carvone it is the ethylenic linking in the hydro-aromatic ring which disappears, and not the second (purely aliphatic) bond, as might have been expected. This behaviour is readily explained if the dispositions of the "residual affinities" in the grouping $-CH=C(CH_3)-\underset{\underset{O}{\|}}{C}-$ are considered.



It will be remembered that Thiele showed that this system,

like the simple diethenoid group, $-CH=CH-CH=CH-$, is abnormal in many of its reactions; for example, sodium bisulphite reacts with unsaturated ketones of this type either not at all (as in the case of carvone) or else with formation of a hydroaromatic sulphonic acid as follows:—



$$-CH=CH.CO- + NaHSO_3 \rightarrow -CH(SO_3Na).CH_2.CO-$$

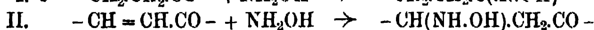
(*cf.* the normal reaction:



$$-CH_2.CH_2.CO- + NaHSO_3 \rightarrow -CH_2.CH_2.C(OH)(SO_3Na)-)$$

Again, hydroxylamine also reacts in two ways with such ketones, yielding either the normal oxime (I) or a hydroxylamino-derivative of the ketone (II):—





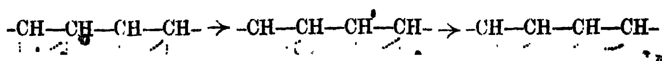
$$\text{I.} \quad -CH_2.CH_2.CO- + NH_2OH \rightarrow -CH_2.CH_2.C(:N.OH)-$$
$$\text{II.} \quad -CH=CH.CO- + NH_2OH \rightarrow -CH(NH.OH).CH_2.CO-$$

Thiele's explanation of these and other similar cases is as follows: he considers that in any ethenoid system $-CH=CH-$ the "affinities" of the unsaturated carbon atoms are not completely occupied in maintaining the double union, and that there is therefore a residue of free excess affinity at each carbon atom. He represents this state of affairs by depicting a simple ethylenic bond as



the dotted lines, which denote the excess or residual affinity possessed by each carbon atom, being termed "partial valencies."

When two such groups are adjacent to each other, it is likely that there will be a mutual effect between the partial valencies concerned, which may be represented thus:

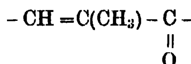


The final effect is to produce a system of carbon atoms in which

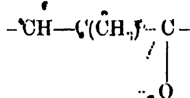
practically all the reactivity is concentrated in the two extreme members.

This hypothesis, which has proved very useful in helping to explain the behaviour of many unsaturated aliphatic compounds, and also the stability and individuality of the aromatic series, is not without application to the terpenes, and of the latter the reduction of *carvone* is a case in point.

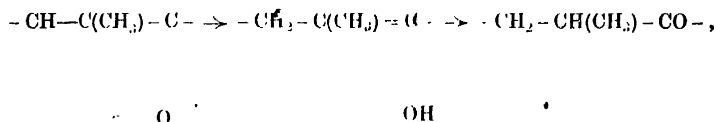
There exists in that ketone the typical "conjugated" system



which, when represented according to the Thiele method, becomes



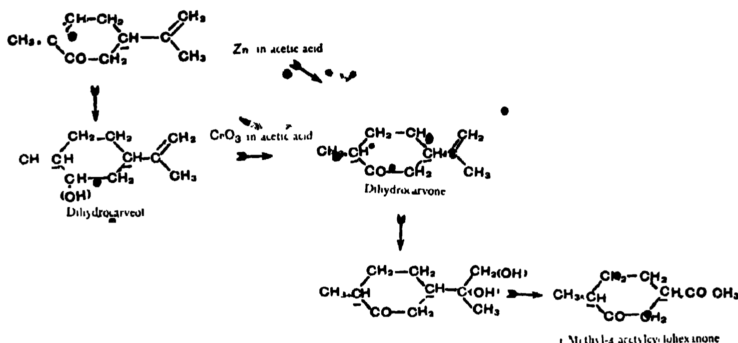
The vulnerable points of this system are thus seen to be the oxygen atom and the carbon atom, to which a free partial valency remains attached. Hence we may suppose that reduction takes place as follows:—



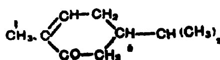
and that the tendency towards addition of hydrogen is assisted by the readiness of oxygen to form the enolic hydroxylic radicle, whereas in the group $>CH-C(CH_3)=CH_2$ there is no oxygen present to promote the reduction.

We pass on to describe the ketones *dihydrocarvone* and *carvotanacetone*, which bear the same relation to *p*-menthene that *carvone* does to *p*-menthadiene, and so possess the molecular formula $C_{10}H_{16}O$.

Dihydrocarvone is formed in small yield when carvone is reduced by zinc dust and acetic acid, and is also produced to some extent when *dihydrocarveol* is oxidized carefully with anhydrous chromic acid in acetic acid solution. Dihydrocarvone is a pleasant smelling liquid, gives carvacrol when boiled with aqueous ferric chloride, and upon oxidation with permanganate, yields first a *ketone alcohol* containing *two* hydroxyl groups, and then a *diketone* which has been shown to be *l-methyl-4-acetylcyclohexanone.* This diketone corresponds in structure with the ketonic alcohol obtained from dihydrocarveol (p. 337), and shows that the constitution of dihydrocarvone must be represented as below :



When *dihydrocarvone* is treated with dilute sulphuric acid, it is partially isomerized to another ketone known as carvotanacetone, which is also obtained by boiling the *trioxyhexahydro-p-cymene* from terpineol (p. 329) with dilute sulphuric acid, *p*-cymene being also produced in the latter case. The new ketone is also produced when the monohydrobromide of *carvone* is reduced with zinc dust. If hydrogen bromide had attached itself to the ethylenic bond adjacent to the carbonyl group in carvone, the ketone produced by reduction would have been *dihydrocarvone* ; since it is the isomeride of the latter ketone which has, as a matter of fact, resulted, it follows that the hydrobromic acid must have attacked the other ethylenic linking, so that *carvotanacetone* should be :



The physical properties of these two isomeric ketones bear out this conclusion. We will illustrate this by reference to their

molecular refractivities, refraction being the physical characteristic which thus far has found greatest application as a physical method, supplementary to chemical evidence, of distinguishing between the constitutions of different compounds.

It is well known that the *molecular refraction*, *Ma*, of a compound, calculated from the refractive index *n* by the Lorentz-Lorenz formula,

$$Ma = \frac{(n_2 - 1) \times \text{Mol. Wt}}{(n_2 + 2) \times \text{density}},$$

gives values closely in agreement with those additively derived by summation of the refractions of the various constituent atoms.

For example, the atomic refraction of *carbon* for the "α" line in the hydrogen spectrum is 2·365; for *hydrogen* for the same line, 1·103; and for *ketonic oxygen*, 2·328. Hence the calculated *molecular refractivity* of acetone, $CH_3.CO.CH_3$, is—

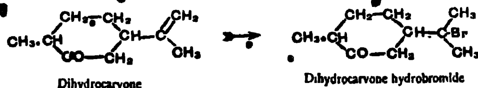
$$(3 \times 2{\cdot}365) + (6 \times 1{\cdot}103) + (1 \times 2{\cdot}328) = 16{\cdot}04$$

whilst that found experimentally is *16·05*. On the other hand, when strongly unsaturated groups occur in a compound, the difference between experimental and theoretical values becomes relatively large, and this *optical anomaly*, as it is called, is exceptionally well marked in the case of substances containing adjacent or "conjugated" unsaturated radicles. Hence it is frequently possible to predict the presence of conjugated unsaturation from the molecular refractivity of a compound.

In the case of the two compounds under discussion, the values are as follows :—

	Ma	*Anomaly.*
Dihydrocarvone (non-conjugated).	45·84	+0·03
Carvotanacetone (conjugated)	46·84	+1·03
$C_{10}H_{16}O$ (calculated for 1 CO group, and 1 ethenoid bond)	45·81	

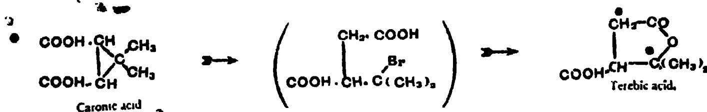
When *dihydrocarvone* is treated with a molecular quantity of hydrogen bromide, addition takes place in accordance with the Markownikow rule already quoted in this chapter (p. 319):



Dihydrocarvone — Dihydrocarvone hydrobromide

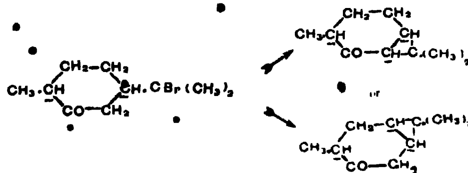
If the latter compound is treated with alcoholic potash, a ketone $C_{10}H_{16}O$ is produced which is an isomeride of, and not identical with, dihydrocarvone.

The new ketone, *carone*, belongs strictly speaking to the class of dicyclic terpenes discussed in chapter xxi., but it may be more conveniently described at this point. On oxidation it breaks down somewhat completely, and yields 1, 1-*dimethyl*-2, 3-*trimethylene carboxylic acid* (*caronic acid*). This acid exists in *cis*- and *trans*-modifications, like most of the trimethylene derivatives, and on treatment with hydrobromic acid it passes into terebic acid:



Caronic acid — Terebic acid.

The formation of *carone* from dihydrocarvone hydrobromide must accordingly take place in one of the following ways:



Chemical evidence tends to support the first of the above formulæ, and this is supplemented by the molecular refractivity of carone, which is $M\alpha = 45 \cdot 26$. The calculated value is $M\alpha = 44 \cdot 11$, so that there is an anomaly of $+ 1 \cdot 15$ units. Now it has been found that physico-chemically the trimethylene ring-system behaves very like an ethylenic group as regards its general unsaturated nature. Hence the optical anomaly argues in favour of the conjugation of the trimethylene group with the carbonyl radicle in carone.

A nearly related isomer of *carone* is *thujone* or *tanacetone*, found in the oils of wormwood, absinthe, and chamomile. There is every reason to believe that thujone also contains a trimethylene ring, whilst on oxidation it yields in succession (i) an *acid*, $C_{10}H_{16}O_3$, (ii) a *diketone*, $C_8H_{14}O_2$, and (iii) *δ-dimethyllævulinic acid*, $(CH_3)_2CH.CO.CH_2.CH_2.COOH$.

The diketone is therefore $(CH_3)_2CH.CO.CH_2.CH_2.CO.CH_3$, and so most probably the acid first formed is

$$\begin{matrix}(CH_3)_2CH \\ \quad\;\; \rangle C{-}CH_2.CH_2.CO.CH_3 \\ COOH.CH \end{matrix}$$

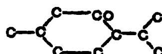
On the other hand, thujone can be transformed to carvacrol, and therefore belongs to the same general type of ketone as carvone and its congeners; moreover, the evidence of oxidation shows that a point of attachment of the trimethylene ring is the carbon atom adjacent to the isopropyl group.

Hence *thujone* must be $CH_3CH\begin{matrix}CH{-}CH_2 \\ CO{-}CH_2\end{matrix}C{-}CH(CH_3)_2$, the trimethylene system and the carbonyl group being non-conjugated, as is indicated by the molecular refractivity, $M\alpha = 44{\cdot}78$ (calculated $M\alpha = 44{\cdot}11$, anomaly $+0{\cdot}67$, as compared with an anomaly of $+1{\cdot}15$ in the conjugated isomer carone).

We will now tabulate the compounds so far described which belong to the carvacrol or carvomenthene type:

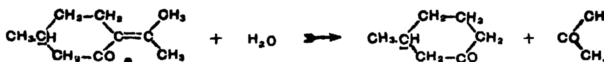
Hydrocarbons	*Alcohols*	*Ketones*
p-Menthane, $C_{10}H_{20}$	Tetrahydrocarveol, $C_{10}H_{19}.OH$ (oxidation →; ← reduction)	Tetrahydrocarvone $C_{10}H_{18}O$
p-Menthenes, $C_{10}H_{18}$ (Carvomenthene) (← dehydration of tetrahydrocarveol)	Dihydrocarveol, $C_{10}H_{17}.OH$ (oxidation →)	Carvotanacetone, $C_{10}H_{16}O$
		Dihydrocarvone, $C_{10}H_{16}O$
p-Menthadienes, $C_{10}H_{16}$ (see section V)	(reduction)	(Carone and thujone)
		Carvone, $C_{10}H_{14}O$

The thymol type of ketone is found in menthone (p. 325) and in another common constituent of oils of pennyroyal and certain mints, *pulegone*, $C_{10}H_{16}O$. Its composition and chemical behaviour indicate that it contains *one* ethenoid bond, whilst on reduction pulegone is converted to menthone. It may therefore be represented in "skeleton" as



The carbonyl residue present in pulegone does not react normally with sodium bisulphite nor with hydroxylamine (compare p. 339), whilst its refractivity suggests the presence of conjugated unsaturation.

Moreover, when heated in sealed tubes with water it yields an equimolecular mixture of acetone and 1, 3-methylcyclohexanone (Wallach). This result can only be explained by assigning the appended structure to *pulegone* :



V. The *p* Menthadienes

We shall confine our study of the monocyclic terpene hydrocarbons of the composition $C_{10}H_{16}$ to those members which are found in nature, especially in the oils of the *Coniferæ* and *Cyperaceæ*, and may commence by a summary of the structure, optical nature, and occurrence of the compounds in question.

Hydrocarbon.	*Optical form.*	*Structure.*	*Chief Occurrence.*
Limonene.	*d*- and *l*-.	Δ 1, 8 (9)-*p*-Menthadiene	*d-Form*, in lemon and orange rinds, and many vegetable oils. *l-Form*, in pine-needles and fir-cones, and in spearmint oils, etc.
Dipentene.	Racemic.	Δ 1, 8 (9)-*p*-Menthadiene.	In pine-needle oil and oils of citron, cubebs, pepper, camphor, nutmeg, and many others.
Terpinolene.	Inactive.	Δ 1, 8 (4)-*p*-Menthadiene.	Not yet found in nature.
Terpinene.	Inactive.	Δ 1, 3-*p*-Menthadiene.	In cardamom and marjoram oils.
α-Phellandrene.	*d*- and *l*-.	Δ 1, 5-*p*-Menthadiene.	Together in oils of fennel (*d*-) and in eucalyptus, pine-needle, and star-anise (*l*-).
β-Phellandrene.	*d*- and *l*-.	Δ 1 (7), 5-*p*-Menthadiene.	

When equal parts of *d*- and *l-limonene* are mixed, the resulting racemic mixture is found to be identical with the terpene *dipentene*, and therefore we need only discuss the evidence for the chemical constitution of the latter. Whereas, however, either of the *limonenes* have only been hitherto prepared directly from the essential oils in which they occur, the racemic variety, *dipentene*, can be prepared from various other terpene compounds. Its chief methods of formation may be classified as follows :—

(i) From the hemi-terpene *isoprene*, C_5H_8, by polymerization.

(ii) By intramolecular rearrangement of the isomeric terpenes *phellandrene* and *pinene*.

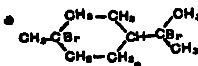
(iii) By distillation of the complex polyterpenes present in rubber.

(iv) By dehydration of the olefinic oxyterpene *linalool* (p. 361).

(v). By dehydration of many monocyclic oxyterpenes such as terpineol, terpin hydrate, and cineol.

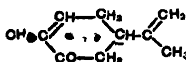
Dipentene forms two series of addition compounds, the one including monohydrogen-bromides and -chlorides, nitrosochlorides, and nitrosites, the other being composed of dihydrogen halides, tetrabromides, dinitrosochlorides, and "nitrosite-nitrosates."

Dipentene dihydrobromide is found to be identical with *cis-terpin dibromide*, which, as we saw on p. 333, must be formnlated as

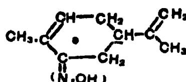


Again, when *dipentene mononitrosochloride* is treated with alcoholic potash, the *oxime of carvone* is formed (dipentene yields in this manner *r*-carvoxime, the *d*- and *l*-limonenes giving respectively *d*- and *l-carvoximes*).

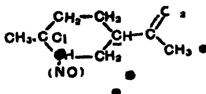
We have proved (p. 338) that *carvone* has the constitution:



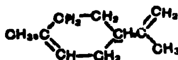
so that its oxime will be:



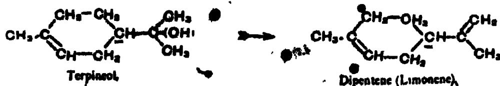
Accordingly, the *nitrosochloride* of *dipentene* must be represented as:



whence we arrive at the following structure for *dipentene* itself:



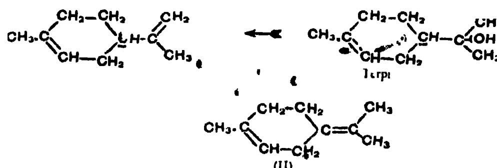
This structure is confirmed by the synthesis of dipentene from terpineol when the latter is heated with potassium hydrogen sulphate:



It will be noticed that, in virtue of Perkin's synthesis of terpineol from its elements, that of dipentene and the limonenes also becomes complete.

If, when terpineol is dehydrated, alcoholic sulphuric acid replaces potassium hydrogen sulphate as desiccating agent, *dipentene* is not produced, but in its place a very unstable terpene, *terpinolene*, is obtained.

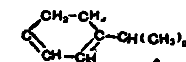
Now it will have been observed above that the simple dehydration of terpineol did not suffice to determine the structure of dipentene, and for this reason, that water may be abstracted from the terpineol molecule in two, and only two, ways :

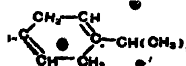


Since it is known from other independent reasons that formula (I) represents dipentene, it follows that (II) is the structure of *terpinolene.*

Terpinolene is a most unstable hydrocarbon, and in presence of traces of acids is rearranged to yet another terpene, *terpinene*; this probably accounts for the non-occurrence of terpinolene in nature.

Terpinene, on the other hand, is the most stable of all the known *p*-menthadienes, and in view of this, and of its formation from terpinolene, it is at present held most probably to possess one of the two following formulæ :—





The symmetrical character of the second structure is a point in its favour, but on the other hand the conjugated diethenoid system present in the first would tend towards stability, and, indeed, the *refractive anomaly* of terpinene, which is fairly high (+0·98 units), points to the correctness of this latter representation.

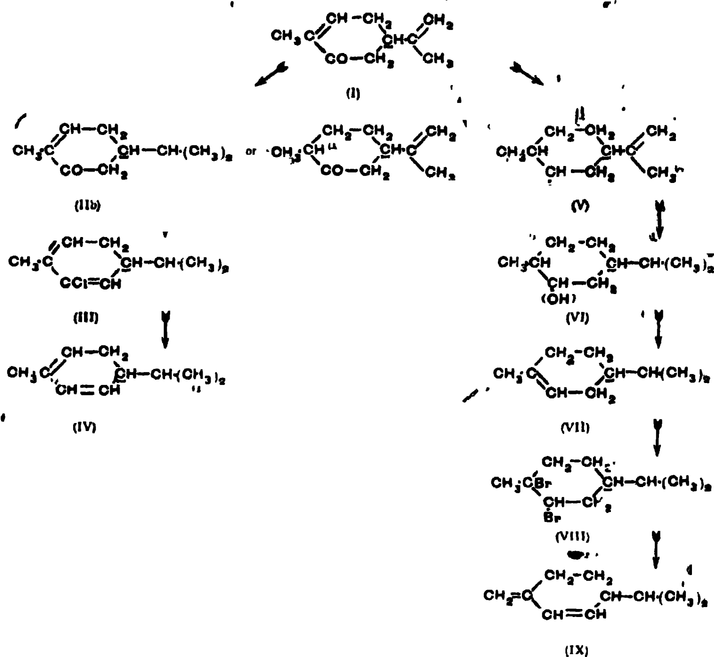
Terpinene is also produced when alcoholic sulphuric acid acts upon pinene, dipentene, phellandrene, or terpin, and from linalool by the action of anhydrous formic acid.

The last pair of *p*-menthadienes to which we shall refer, the *phellandrenes*, were regarded as a single terpene for many years, but Semmler showed in 1903 that the supposed hydrocarbon was a mixture of at least two isomers, and succeeded in effecting a partial separation of these two bodies. Two or three years later, syntheses from carvone of each form of phellandrene were published, due respectively to Harries and to Kondakow.

Harries' synthesis of the *a-phellandrene* is as follows:

Carvone (I) forms a monohydrobromide, in which the bromine can be replaced by hydrogen on reduction with zinc, giving a *p-menthene ketone*, (IIa or IIb). The product is identical with *carvotanacetone* (p. 341), and therefore possesses the constitution (IIb). This reacts in the *enolic* condition with phosphorus pentachloride, whereby the *chloro*-derivative (III) is formed, and this by reduction with zinc dust gives *a-phellandrene* (IV).

On the other hand, Kondakow reduced *carvone* (I) to *dihydrocarveol* (V), and thence to *tetrahydrocarveol* (VI), which by dehydration gives *carvomenthene* (VII., p. 328). *Carvomenthene dibromide* (VIII) gives *β-phellandrene* (IX) when warmed with alcoholic alkali.



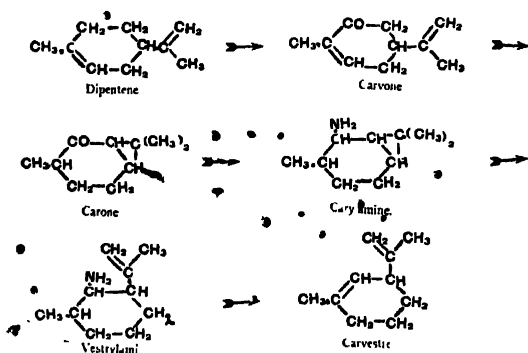
VI. The *m*-Menthadienes

There are two menthadienes of the *meta*-series (*i.e.* connected with *m*-cymene rather than with *p*-cymene) which must receive mention. Both possess the same constitution, but whilst one (*carvestrene*) is racemic, the other (*sylvestrene*) is *dextro*-rotatory. They occur in somewhat small amount in German and Swedish pine-needle oil, and also occasionally in Finnish turpentine.

Carvestrene can be produced indirectly from the *p*-menthadiene *dipentene* as follows :—

Dipentene is first converted to carvone (p. 347), and the latter ketone then transformed to carone as described on p. 343. The *oxime* of *carone* yields an amine, *carylamine*, when reduced, and if the latter amine is heated with alcoholic hydrogen chloride,

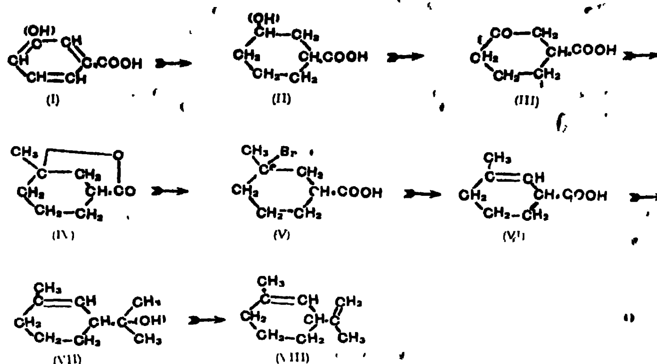
the trimethylene ring (of carone) is ruptured, and an isomeride results. The new amine, known as *vestrylamine*, is not, however, identical with the reduction product of dihydrocarvoxime (*dihydrocarvylamine*), and must therefore be formulated as a *m*-menthane derivative. Its hydrochloride, when distilled, decomposes into ammonium chloride and *carvestrene*:



Both *carvestrene* and *sylvestrene* have recently been prepared synthetically by Perkin in a manner entirely analogous to his complete synthesis of dipentene.

m-Oxybenzoic acid (I) was reduced by sodium in alcoholic solution to *hexahydro-m-oxybenzoic acid* (II), which by careful oxidation gave *γ-ketohexahydrobenzoic acid* (III). Treated with a molecular quantity of magnesium methyl iodide, the latter acid gave *γ-oxyhexahydro-m-toluic lactone* (IV); hydrogen bromide reacted additively with this lactone, yielding the bromo-derivative (V) which by warming with pyridine was transformed to *Δ^2-tetrahydro-m-toluic acid* (VI). The methyl ester of this acid was again treated with the above Grignard reagent (exactly as in the corresponding terpineol synthesis), and the unsaturated alcohol (VII) obtained was heated in presence of potassium hydrogen sulphate, when water was eliminated, and *carvestrene* (VIII) resulted.

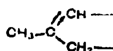
By resolution of the *Δ^2-tetrahydro-m-toluic acid*, the *dextro*-form was isolated, and this, when submitted to the sequence of reactions (VII) and (VIII), yielded a *m*-terpene identical in all respects with *sylvestrene*.



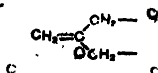
VII. Mutual Relations between the Monocyclic Terpenes

Of recent years many other synthetic menthadienes of both series have been prepared, notably in the Manchester laboratories; indeed, the number obtained is fast approaching that of the isomerides demanded by theory. Since these compounds, however, are of purely theoretical interest, they will not be further dealt with in the present volume.

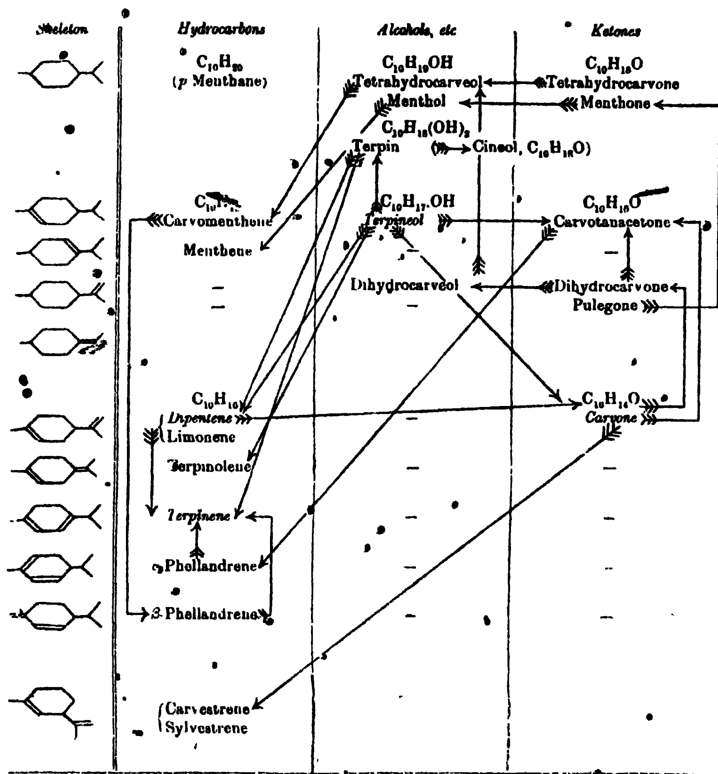
One curious feature of all the natural terpenes may be pointed out, namely, that one of the ethenoid bonds is invariably found at the carbon atom united with the methyl group, most usually in the system:



but occasionally also in a methylenic form:



It may be found convenient if we conclude this chapter by a table illustrating the more striking connexions between the monocyclic terpene compounds; in the first column is given a "skeleton formula" by which the degree of unsaturation of the related compounds may be seen at a glance.



CHAPTER XX

NON-CYCLIC (OR OLEFINIC) TERPENES

I. Isoprene, C_5H_8

THE first compound of the open-chain series which we must consider is not a true terpene, but a *hemiterpene*, its formula being C_5H_8, and not $C_{10}H_{16}$. The substance in question, *isoprene*, is nevertheless most important, for, although it is never found in nature, it is most probably the original substance from which the many isomerides of the formulæ $C_{10}H_{16}$ and $C_{15}H_{24}$ are directly derived.

The intimate connexion of isoprene with the natural terpenes is emphasized by the fact that many of them, especially india-rubber and the different turpentine oils, break down into this compound when heated at a temperature of 500-700° C.

Again, when isoprene, which is a mobile liquid boiling at 37°, is heated to 300°, it is polymerized to a bimolecular compound, $C_{10}H_{16}$, which possesses most of the properties of *dipentene*, whilst on standing in bright sunlight for a long period it is converted into a gummy elastic body which very closely resembles rubber.

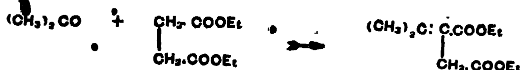
At the present time, "artificial rubber" is manufactured in Germany to some extent by decomposing crude turpentine oil into isoprene, and subsequently repolymerizing it at the ordinary temperature.

Isoprene is a very unsaturated hydrocarbon, and yields a di- and a tetra-bromide by addition of bromine at a low temperature.

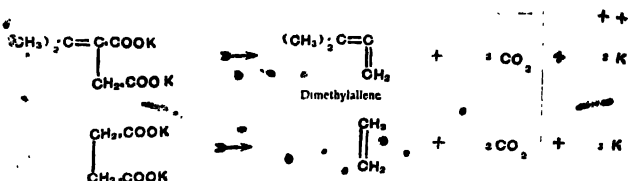
On the other hand, there is no evidence that isoprene is an acetylenic compound, and, indeed, its constitution as a conjugated di-ethenoid hydrocarbon has been made clear by two syntheses :

(i) In 1897, Ipatiew prepared isoprene from the isomeric dimethylallene, the latter hydrocarbon being itself synthesized in the following manner:

Diethyl succinate and acetone condense in presence of sodium ethylate, forming the ester of *dimethylitaconic acid* :—



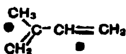
When the potassium salt of this acid is electrolysed, *dimethylallene* is produced (just as electrolysis of potassium succinate yields ethylene):



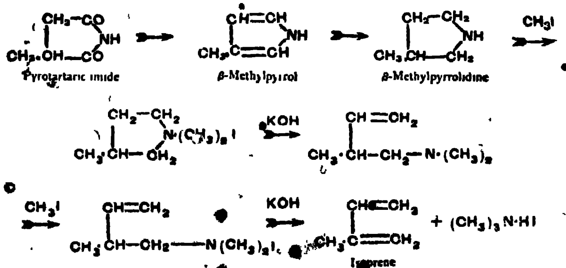
Dimethylallene yields a *dihydrobromide* addition product which, in accordance with the Markownikow rule, may be formulated as:



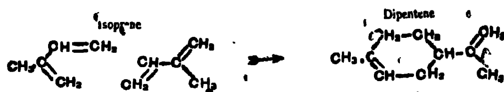
and when the latter is treated with alcoholic potash, *isoprene* results:



(ii) In 1898, Euler obtained *isoprene* by the "exhaustive methylation" of *β-methylpyrrolidine*, itself produced synthetically from methylsuccinic (pyrotartaric) acid (compare pyrrol syntheses, chap. iv. p. 42).

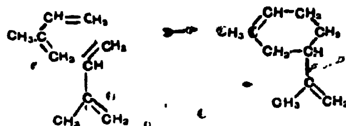


The polymerization of isoprene to dipentene can easily be represented as follows :—

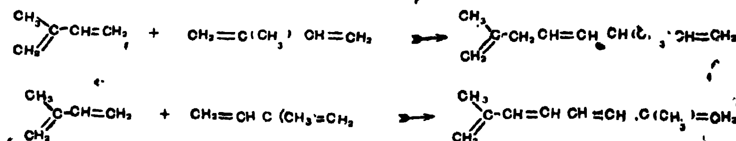


On the other hand, it is easy to see how other isomerides of the composition $C_{10}H_{16}$ might equally readily be formed ; for instance :—

(i) A *m*-menthadiene :

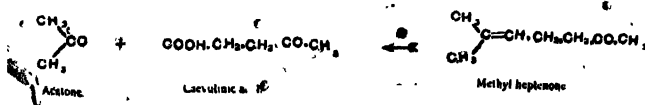


(ii) A non-cyclic terpene :

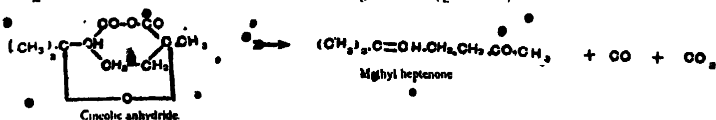


II. Methyl Heptenone

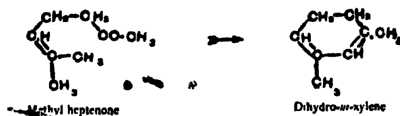
We will approach the real olefinic terpenes by consideration of a nearly related compound of the formula $C_8H_{14}O$, which occurs associated with the former bodies in various essential oils, such as those of geranium, lemon, rose, etc. It is an unsaturated ketone known as *methylheptenone*, and its constitution is at once gathered from its oxidation products, which are acetone and *lævulinic acid in molecular proportions. This fact enables us to build up a formula for the ketone as follows :—*



This structure readily explains the production of methyl heptenone from *cineolic acid anhydride* (p. 335) :

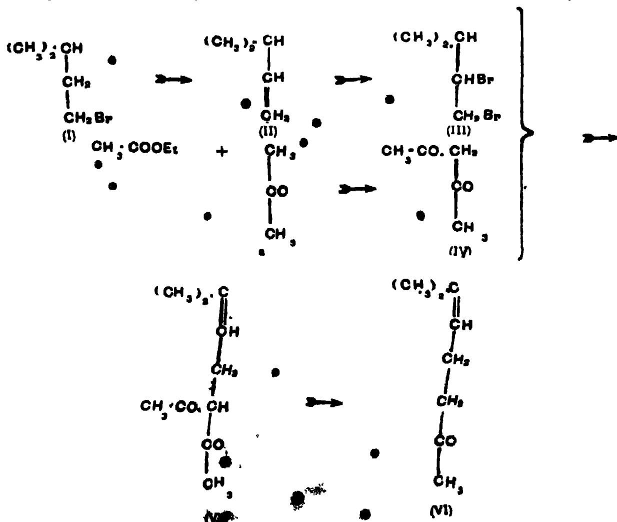


and also renders obvious the production of *dihydro-m-xylene* when the ketone is treated with 75 per cent. sulphuric acid :



Finally, we may quote a synthesis of *methyl heptenone* by Barbier and Bouveault (1896) :

Isoamylenedibromide (III), prepared by addition of bromine to the *isoamylene* (II), obtained from *isoamyl bromide* (I), is condensed with the monosodium salt of *acetylacetone* (IV) (from the Claisen condensation of acetone with ethyl aceate). The product (V) is boiled with alcoholic potash, when *methyl heptenone* (VI) and acetic acid are produced. It will be seen that this process is simply a variant of an "acetoacetic ester" synthesis.

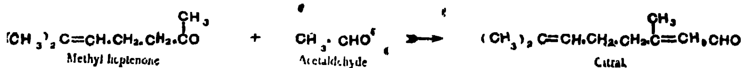


The importance of methyl heptenone lies in its capability of transformation into the olefinic terpenes of the citral type, to which we now pass.

III. The Citral Group

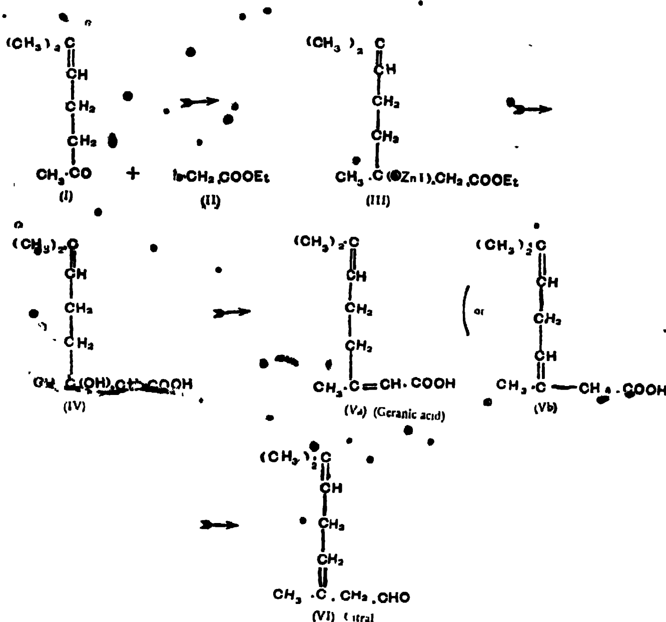
The most abundant of the naturally occurring olefinic terpene derivatives is the aldehyde *citral*, an optically inactive compound found to the extent of about 70-80 per cent. in oil of lemon grass, and also in the oils of oranges, mandarins, verbena, balm, bay, and many other shrubs. Citral is readily isolated in the pure condition from any of these essential oils by shaking with sodium bisulphite, and, after separating the well-defined addition compound, regenerating the aldehyde by gentle warming with alkali carbonate.

Citral possesses the formula $C_{10}H_{16}O$, and its constitution is rendered evident by the change it undergoes when boiled with strong sodium carbonate solution; under these conditions a kind of hydrolysis takes place, a molecule of water being added, and a mixture of methyl heptenone and acetaldehyde resulting:

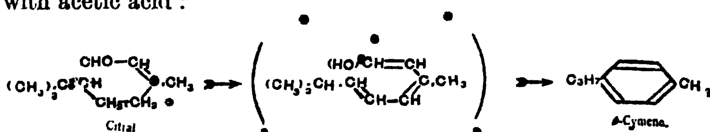


Citral has been synthesized from an acid, *geranic acid*, by Tiemann (1898); geranic acid in turn was synthetically prepared from *methyl heptenone* in 1896 by Barbier and Bouveault

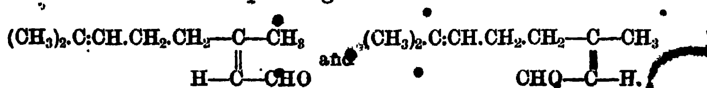
Methyl heptenone (I) is treated with *iodoacetic ester* (II) in presence of powdered zinc, when a similar reaction to the "Grignard" process takes place at the carbonyl group, and the double metallo-organic derivative (III) is formed. By the action of water and subsequent hydrolysis the acid (IV) is produced, which by heating with acetic anhydride gives *geranic acid* (V*a* or V*b*). Since boiling alkali carbonate resolves geranic acid into methyl heptenone and acetic acid, it is plain that the acid has the constitution (V*a*). When its calcium salt is distilled with calcium formate, *citral* (VI) results, just as acetaldehyde results when a mixture of calcium acetate and formate is submitted to dry distillation:



Citral is transformed to *p*-cymene by loss of water when boiled with acetic acid :



The citral found in nature has been proved to be a mixture of two stereo-isomers. Since there is no possibility of the existence of optically active forms of the compound, it seems likely that the isomerism is of the *geometrical* type, and from investigation of the related alcohols *geraniol* and *nerol* (which are described below), it appears that the two forms of citral may be represented as "*cis-trans*" isomerides corresponding to the formulæ :



Alcohols related to citral. Three isomeric alcohols, $C_{10}H_{17}.OH$, which are found widely distributed in nature, each yield the aldehyde *citral* when submitted to acid oxidation. These are *geraniol, nerol,* and *linalool.* The two former are believed to be stereoisomeric varieties of the same alcohol, whilst *linalool* differs slightly from these in chemical constitution.

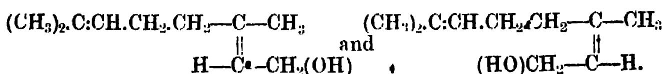
Geraniol is found chiefly in the oils of geranium, citron, and lemongrass; *nerol* occurs associated with it in those of neroli, lavender, spike, and others.

The *acetates, valerianates,* and *tiglates* of both are also frequently present with the alcohols themselves.

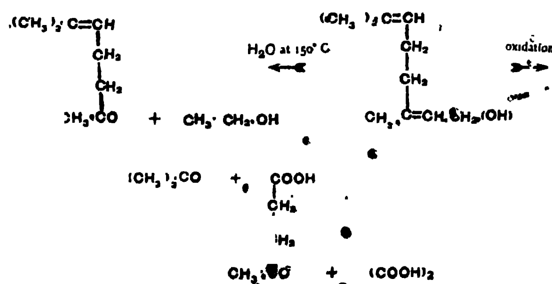
Both geraniol and nerol are obtained when citral is reduced with sodium amalgam, and the aldehyde is similarly produced by their oxidation with the theoretical amount of chromic acid.

When heated under pressure with water, *geraniol* or *nerol* yield methyl heptenone and ethyl alcohol, whilst by oxidation with acid permanganate, acetone, lævulinic acid, and oxalic acid are produced.

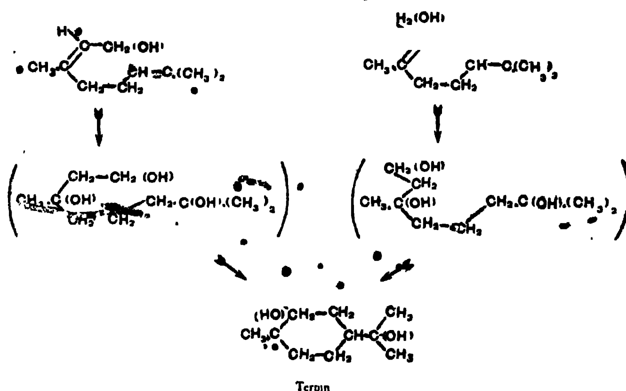
It is therefore assumed that the two alcohols are geometrical isomerides corresponding to the stereoisomeric *citrals* :



This conclusion accords also with the above hydrolytic and oxidation reactions :

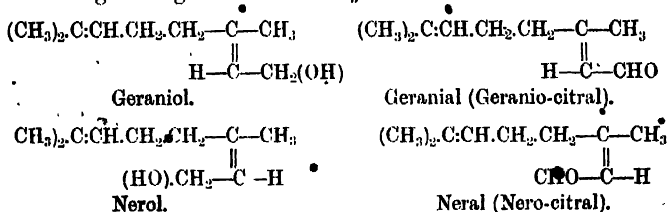


When heated with dilute sulphuric acid, both *geraniol* and *nerol* yield *terpin* (*hydrate*), the latter very much more readily than the former. Now it will be seen from the appended formulæ that one of the geometrical isomerides is much more adapted to form the cyclohexane ring-system than the other :



Terpin

Nerol is therefore assigned the structure (*a*) and *geraniol* the configuration (*b*) ; moreover, the relative quantities of the two forms of citral formed by oxidation of geraniol and nerol are different, and consequently that preponderating in the oxidation of *nerol* is given the structure shown below, and is known as nerocitral or *neral*; whilst the other, formed in greater amount from geraniol, is represented as the geometrical isomeride of *neral*, and designated geranio-citral or *geranial* :

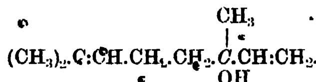


Linalool, on the other hand, occurs in optically active forms, and is widely distributed in the oils of coriander, bergamot, neroli, petitgrain, thyme, lavender, and others. *Linalyl a*

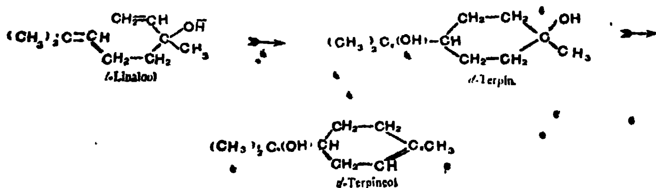
propionate, butyrate, and *valerianate* frequently accompany the alcohol in small quantities.

Racemic linalool is formed to a certain extent when geraniol or nerol are heated to 200° C. with water in an autoclave, whilst, on the other hand, the natural optically active linalools give a mixture of geranyl and neryl acetates when boiled with acetic anhydride containing acetic acid.

The only isolable products of the oxidation of *linalool* are acetone and lævulinic acid; and from this fact, taken in conjunction with the interconvertibility of linalool and geraniol-nerol, it is argued that linalool is a tertiary alcohol of the formula:



An apparent argument against this formula is the conversion of *l-linalool* to *d-terpin* (*hydrate*) by the action of dilute sulphuric acid; for, since the *d-terpin* can be dehydrated to *d-terpineol*, in which the asymmetric carbon atom of *l-linalool* has disappeared (although it is true that a new (plausibly racemic?) one has been introduced), it is difficult to understand the optical activity of the terpineol produced:



The matter is not yet cleared up.

Dipentene, terpinene, and other products of the monocyclic terpene series are also obtainable under different conditions from the three alcohols described above, but the formation of these products depends on the primary production of *terpin hydrate,* and therefore need not be further enlarged upon.

Hydrocarbons related to citral. Dehydration of *geraniol* by potassium hydrogen sulphate at 170° produces amongst other substances a hydro-

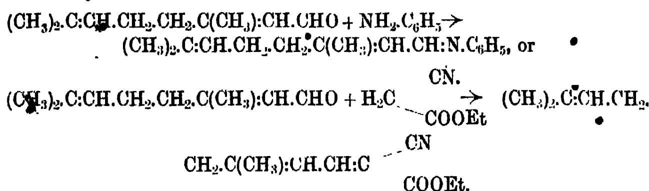
carbon of the formula $C_{10}H_{16}$, known as *anhydrogeraniol*. This compound contains three ethenoid bonds, and is therefore an olefinic terpene, but its formula is uncertain. Isomeric with it is *myrcene*, also a triolefinic compound, which is found in oils of bay and of laurel.

A diolefinic hydrocarbon of unknown structure, *linaloolene*, $C_{10}H_{18}$, results from the reduction and subsequent dehydration of linalool.

IV. Some Cyclic Derivatives of Citral

Citral is the root-substance of certain cyclic compounds which are, nevertheless, not monocyclic terpenes but are derived from 1-*methyl-3-gem *-dimethyltetrahydrobenzene*, and contain in a side-chain attached to the nucleus an aldehydic or ketonic group.

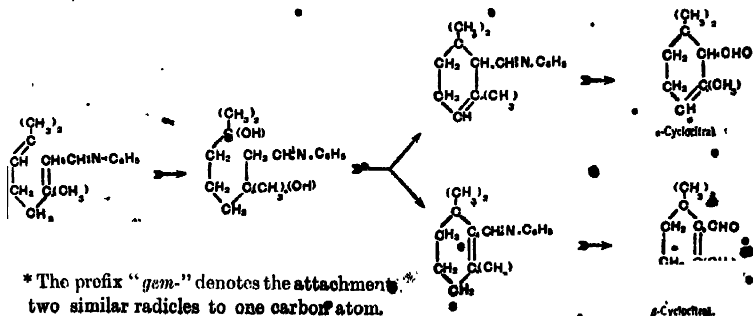
The simplest types of these intramolecularly condensed citrals are the α- and *β-cyclocitrals*, which are readily formed by warming citral with aniline or cyanacetic ester. The first product is produced by the usual condensation :



$$(CH_3)_2.C:CH.CH_2.CH_2.C(CH_3):CH.CHO + NH_2.C_6H_5 \rightarrow$$
$$(CH_3)_2.C:CH.CH_2.CH_2.C(CH_3):CH.CH:N.C_6H_5, \text{ or}$$

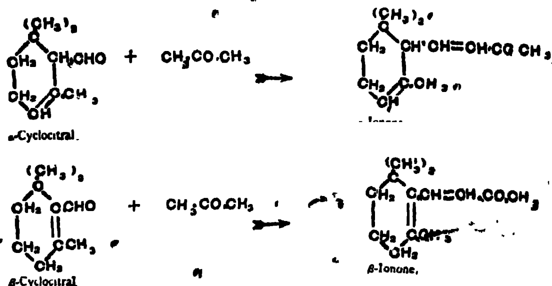
$$(CH_3)_2.C:CH.CH_2.CH_2.C(CH_3):CH.CHO + H_2C\begin{matrix} CN. \\ COOEt \end{matrix} \rightarrow (CH_3)_2.C:CH.CH_2.$$
$$CH_2.C(CH_3):CH.CH:C\begin{matrix} CN \\ COOEt. \end{matrix}$$

The ring-system is then closed by addition and re-elimination (in two possible ways) of two molecules of water, and the mixture of the anils or cyanacetyl derivatives of the two isomerides yields the free *cyclocitrals* by treatment with dilute mineral acid :

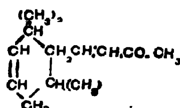


* The prefix "*gem-*" denotes the attachment of two similar radicles to one carbon atom.

By further condensation with acetone in presence of baryta water, each of the cyclocitrals yields the corresponding α- and β-*ionones*, which are commercially valuable as a substitute for oil of violets in perfumery :



The actual constituent of oil of violets and orris oil which gives rise to the characteristic perfume is *irone*, $C_{13}H_{20}O$, isomeric with the above, and represented by the formula :



V. The Citronellal Group

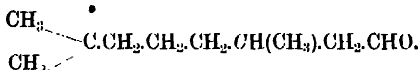
The aldehyde *citronellal*, $C_{10}H_{18}O$, is an optically active substance which occurs (as the *dextro*-rotatory variety) in eucalyptus oil, balm oil, and lemon oils.

By careful oxidation it yields the corresponding acid, *citronellic acid*, and by reduction, *citronellol*, $C_{10}H_{19}(OH)$, an unsaturated monohydric alcohol, which is found (usually in the *lævo*-form) in oil of geranium and oil of rose.

It might be supposed that these compounds correspond respectively to the dihydro-reduction products of *citral*, *geranic acid*, and *geraniol*; but geranic acid, when reduced, yields an acid,

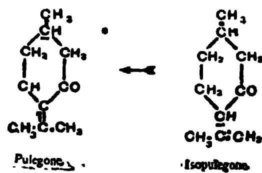
rhodinic acid, $C_{10}H_{18}O_2$, which by further treatment gives the corresponding aldehyde, *rhodinal*, $C_{10}H_{18}O$, and alcohol, *rhodinol*, $C_{10}H_{19}(OH)$, and these products are apparently not identical, nor even stereoisomeric, with the *citronellal* compounds.

Since *citral* is represented as $(CH_3)_2.C:CH.CH_2.CH_2.C(CH_3):CH.CHO$, *rhodinal* would most probably be $(CH_3)_2.C:CH.CH_2.CH_2.CH(CH_3).CH_2.CHO$, whereas *citronellal* appears from its reactions to be



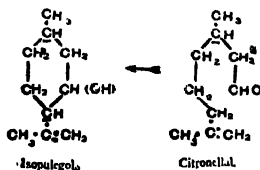
The reactions in question are as follows:

(i) When treated with acetic anhydride, *citronellal* is converted to the acetate of *isopulegol*; the latter cyclic alcohol can be oxidized to a ketone, *isopulegone*, which by simple isomerization is transformed into *pulegone*:



Pulegone. Isopulegone.

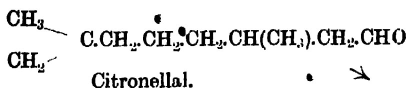
Isopulegol must therefore be formulated as below, and this leads to the appended formula for the isomeric *citronellal*:

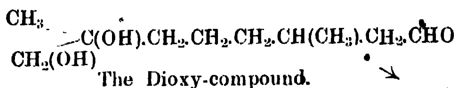


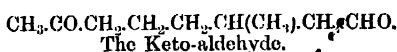
Isopulegol. Citronellal.

(ii) The suggested formula is confirmed by the careful oxidation of citronellal by potassium permanganate in cold aqueous acetone; the first product is a dioxy-citronellal, which is next transformed to a keto-aldehyde containing one carbon atom less than the original citronellal. We have met this characteristic reaction of the *methylene* radicle $>C:CH_2$ in connexion with terpineol and other compounds of the monocyclic series,

and it is evident that the production of the keto-aldehyde is readily accounted for by the above constitution :







VI. Relations between the Olefinic Terpenes

We append a table showing the chief connexions between the various compounds of the non-cyclic terpene series.

	Monoethylenic	*Diethylenic*	*Triethylenic*	
Hydrocarbons	$C_{10}H_{20}$	$C_{10}H_{18}$	$C_{10}H_{16}$	
	—	Linaloolene	Anhydrogeraniol	
Alcohols	$C_{10}H_{19}(OH)$	$C_{10}H_{17}(OH)$		
	Rhodinol Citronellol	*Linalool* *Geraniol* *Nerol*	—	Methyl heptenone + ethyl alcohol
Aldehydes	$C_{10}H_{18}O$	$C_{10}H_{16}O$		
	Rhodinal *Citronellal*	*Citral*	—	Methyl heptenone + acetaldehyde
		$C_{13}H_{20}O$ (Ionones)		
Acids	$C_{10}H_{18}O_2$	$C_{10}H_{16}O_2$		
	Rhodinic acid Citronellic acid	Geranic acid	—	Methyl heptenone + acetic acid

CHAPTER XXI

POLYCYCLIC TERPENES: DERIVATIVES OF PINENE CAMPHOR, AND FENCHONE; AND THE SESQUI-TERPENES

I. DERIVATIVES OF PINENE

A. THE CONSTITUTION OF PINENE.

THE most abundant of the naturally occurring dicyclic terpenes (and, indeed, of all the terpene derivatives) is the hydrocarbon *pinene*, $C_{10}H_{16}$, which is the chief constituent of turpentine oils. The *dextro*rotatory form of pinene, sometimes termed *australene*, is found in the oils exuded from Russian American, German, and Swedish pines, and also in cypress, star-anise, laurel, fennel, coriander, myrtle, eucalyptus, and many other oils. *l*-Pinene, or *terebenthene*, occurs in French pine oils and in pine-needle, hemlock, cajeput, valerian, thyme, spearmint, parsley, and a number of other oils.

The optically active forms can only be purified by repeated fractionation under diminished pressure, whilst *inactive* pinene is readily obtained pure by treating the alcoholic solution of the nitrosochloride of either active variety with aniline.

Pinene is unsaturated, but only forms a monohydrochloride and a dibromo-addition product, and a mononitrosochloride. The inference is that only one ethenoid bond is present, and therefore, in view of its formula $C_{10}H_{16}$, it is certain that pinene must possess a double or dicyclic ring-system.

Pinene is very readily oxidized, and even by simply standing in presence of moist air it is converted to an unsaturated glycol known as *sobrerol*. At the same time small quantities of hydro-

gen dioxide are produced, and the emulsion of air-oxidized pinene and water consequently finds application, under the name of "Sanitas," as a pleasant-smelling antiseptic and disinfectant.

Pinene hydrochloride is a solid crystalline compound, very much resembling camphor (p. 373) in appearance and smell, and often sold as "artificial camphor." When heated with anhydrous sodium acetate, this compound is converted to a hydrocarbon, $C_{10}H_{16}$ which, however, is not pinene, but an isomeride known as *camphene* (p. 384). Moreover, when pinene hydrochloride is treated with a solution of silver acetate, silver chloride is removed and the resulting product is the *acetate* of an alcohol, *isoborneol*, of the camphor series, and when oxidized with nitric acid, *camphoric* and other acids of the camphor series result.

The *pinene* and *camphor* groups of the dicyclic terpenes are thus very intimately related.

On the other hand, by various processes pinene can be readily transposed to *p-cymene*, *carvacrol* (p. 336), or a number of the *p-menthadienes*. It is therefore plain that in pinene there exist the elements, at all events, of a methyl and of an isopropyl group, which are separated on either hand by a chain of two carbon atoms :

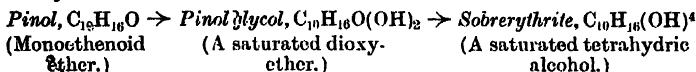


We must next study some of the oxidation products of pinene, and from these we shall be able to deduce a very probable formula which represents satisfactorily its general behaviour. (As a matter of fact, the choice of suitable formulæ is much more difficult in the dicyclic than in the monocyclic terpene series, and in the case of pinene and several other members thereof, a number of rival formulæ still contend for the representation of these substances ; we shall, as a general rule, restrict our discussion in each case to the structure which appears to meet with most general support from the authorities in this field.)

The oxidation of pinene takes place in two main stages :

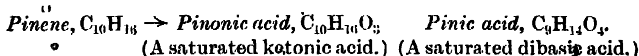
(i) Atmospheric oxidation produces the unsaturated glycol, *sobrerol*, $C_{10}H_{16}(OH)_2$; this, by the action of dilute acids, loses a molecule of water and forms *pinol*, $C_{10}H_{16}O$, an unsaturated compound in which the oxygen, like that in cineol (p. 334), is of ether-like or oxide type, and not alcoholic nor carbonylic.

(ii) When *pinol* is carefully oxidized at 0° with 1 per cent. aqueous permanganate, and subsequently with a more concentrated solution of the same reagent at the ordinary temperature, the following products are successively obtained:

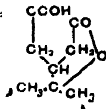




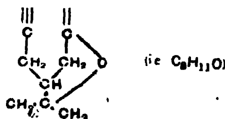
(iii) When *pinene* itself is oxidized by potassium permanganate, the products formed in the first place are:



Reaction (ii) shows a connexion between *pinene* and *terpenylic acid*, and we already know that the latter compound is constituted as follows:—

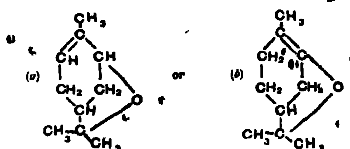


The lactonic oxygen atom in the latter acid corresponds almost certainly with the ethereal oxygen of pinol, and, omitting the parts of the terpenylic acid molecule which are obviously due to oxidation, we are left with the following skeleton of the molecule of *pinol* as that part which has escaped oxidation:

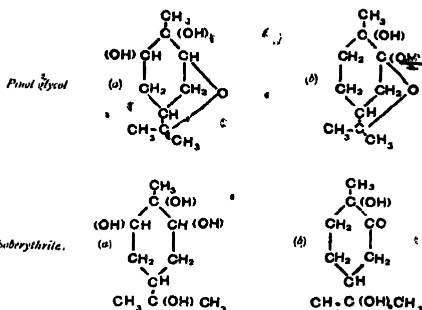


Since *pinol* has the composition $C_{10}H_{16}O$, we have now to account for (C_2H_5), out of which residue we must allow for a group (CH—C) in a "*para*"-position to the isopropyl (or rather, in this case, the *gem-dimethyl*) residue.

This reduces the number of possible formulæ for *pinol* to two, namely:

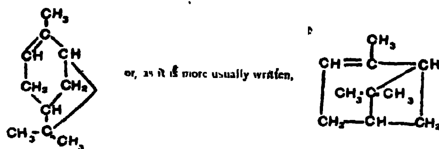


Let us now construct the corresponding formulæ for the saturated glycc and the saturated tetrahydric alcohol derived from pinol, in accordanc with each of the above suggested structures for the latter compound:

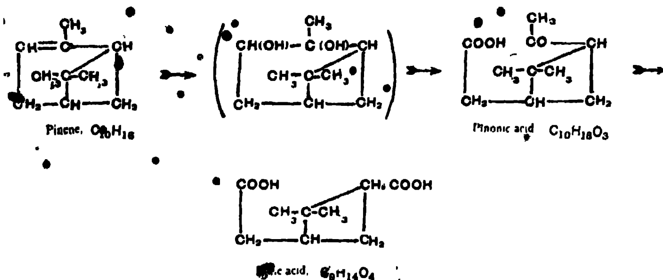


Evidently, then, the structure (*b*) would not yield a tetrahydric alcoho at all, but a dioxyketone, and thus it is argued that (*a*) is the true formul for pinol. This harmonizes with the fact that *sobrerythrite* is a sweet somewhat sugar-like compound, since in the *sobrerythrite* (*a*) formula we find three adjacent alcoholic radicles, and it is well known that accumulation of such groups is frequently accompanied by sugar-like properties.

Wagner, who is responsible for most of the experimental work and theoretical conclusions in connexion with the above formula for *pinol*, infers that *pinene* itself is



We are now able to derive the structures of the two acids formed by oxidation of *pinene* :—



B. RELATIONS BETWEEN PINENE AND THE *p*-MENTHADIENE SERIES.

The following are the chief reactions by which it is at present possible to pass between the pinene and the monocyclic *p*-terpene compounds.

(i) *Formation of pinene derivatives from the monocyclic compounds.*

(*a*) Wallach showed that when *terpineol dibromide* is treated with sodium ethylate, *pinol* is formed amongst the products of the reaction.

(ii) *Conversion of pinene derivatives to the monocyclic compounds.*

(*a*) *Pinene*, with dilute hydrochloric acid, yields *dipentene*.

(*b*) *Pinene*, with alcoholic sulphuric acid, yields *terpinene*.

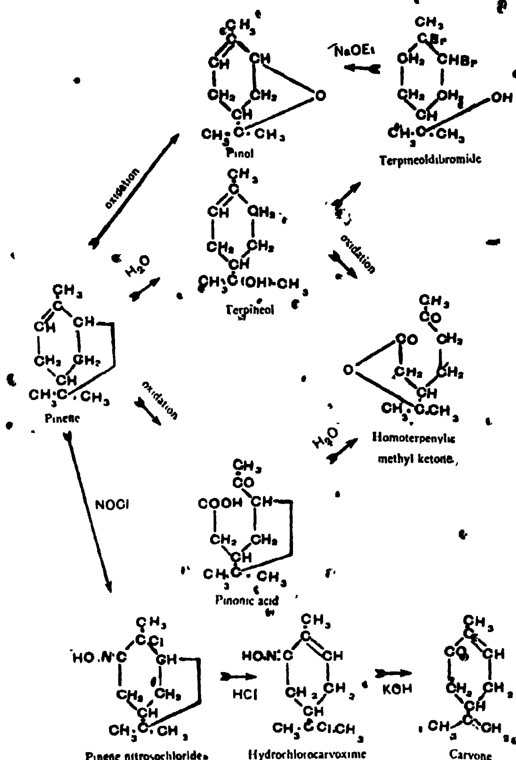
(*c*) *Pinene*, with dilute aqueous sulphuric acid, yields *terpin hydrate*.

(*d*) *Pinene*, warmed with a mixture of acetic and sulphuric acids, yields *terpineol*.

(*e*) *Pinonic acid*, warmed with a mixture of acetic and sulphuric acids, yields *homoterpenylic methyl ketone*.

(*f*) *Pinene nitrosochloride*, with dilute hydrochloric acid, yields *hydrochlorocarvoxime*, which is transposed by dilute alcoholic potash to *carvone*.

The production of *dipentene*, *terpinene* and *terpin hydrate* as formed in the above reactions is natural if we grant that *terpineol* is produced in the first place. The remaining transformations may be structurally illustrated as follows :—



II. Derivatives of Camphor

A. The Properties of Camphor, $C_{10}H_{16}O$.

Camphor is the most abundant of the somewhat numerous natural ketones of the composition $C_{10}H_{16}O$; it is optically

active, and in nature the *dextro*rotatory form is the more frequently found, notably in camphor oil and leaves, cinnamon root, sassafras leaves, and rosemary. *l-Camphor* has only been noticed hitherto in the oils of feverfew and of tansy. Camphor is a crystalline compound with a very refreshing and pleasant odour; it melts at 175° and boils at 204°, but even at the ordinary temperature it sublimes with great ease. Its specific rotatory power is $[\alpha]_D = \pm 44{\cdot}2°$.

Its chief chemical reactions are as follows :—

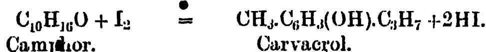
I. *Conversion to Aromatic Compounds*

(i) When distilled with phosphorus pentoxide or zinc chloride, camphor yields abundance of *p-cymene*; this is simply a case of dehydration:



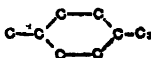
$$\underset{\text{Camphor.}}{C_{10}H_{16}O} \longrightarrow \underset{p\text{–Cymene.}}{CH_3.C_6H_4.C_3H_7} + H_2O.$$

(ii) When treated with iodine, camphor is converted by mild oxidation to *carvacrol*:



$$\underset{\text{Camphor.}}{C_{10}H_{16}O} + I_2 = \underset{\text{Carvacrol.}}{CH_3.C_6H_3(OH).C_3H_7} + 2HI.$$

Hence, like pinene, camphor contains methyl and isopropyl residues in "para-" positions to one another, and the relative position of the ketonic group to these is shown by the reaction with iodine; *camphor* thus possesses the following "skeleton" of carbon atoms :—



II. *Addition Reactions*

Camphor does not unite additively with the halogen acids, the halogens, or nitrosyl chloride; we may therefore assume that no ethylenic bond is present, so that, as a saturated monocyclic ketone of the hexahydro-*p*-cymene series possesses the formula $C_{10}H_{18}O$ (camphor being $C_{10}H_{16}O$), we may argue that the camphor nucleus must be of a dicyclic nature.

III. *Substitution Reactions*

Camphor is sufficiently stable to undergo substitution when treated under suitable conditions with chlorine, bromine, sulphuric acid, and certain other reagents. Two isomeric series of chloro- and bromo-camphors, and of camphorsulphonic acids, have thus been prepared; the isomerism is one of position, and not due to steric influences, and the two series are known respectively as the π- (or α-) and β-substituted camphors.

IV. *Reactions of the Ketonic Group*

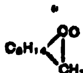
(*a*) *General.*

(i) Camphor does not unite with sodium bisulphite.

(ii) Camphor yields an *oxime* (m.p. 118°) with hydroxylamine, a liquid *phenylhydrazone* with phenylhydrazine, and a *semicarbazone* (m.p. 236°) with semicarbazide, $NH_2.CO.NH.NH$.

Camphoroxime, when reduced by sodium amalgam, gives a mixture of amines (the *bornylamines*, p. 383) of the formula $C_{10}H_{17}.NH_2$.

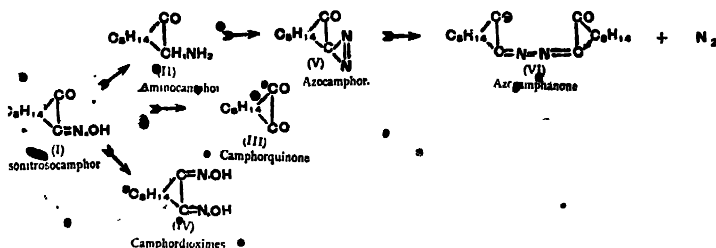
(iii) Camphor reacts with sodium, forming a *monosodium* derivative, $C_{10}H_{15}ONa$; the latter, by interaction with benzoyl chloride, produces *benzoylcamphor*, $C_{10}H_{15}O.(CO.C_6H_5)$. Evidently, then, a hydroxylic (*i.e.* *enolic*) form of camphor can exist, so that we must accept the presence of a *ketomethylene grouping*, $-CH_2.CO-$, in the formula of the ketone, and we may thus portray it as



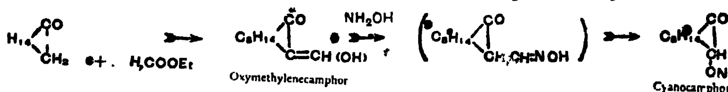
(*b*) *Reactions of the ketomethylene group, $-CH_2.CO-$, in camphor.*

(i) When amyl nitrite and alcoholic sodium ethylate act upon camphor, an *isonitroso*-compound is produced.

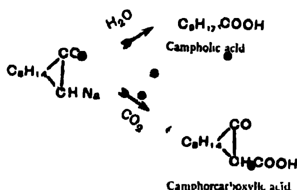
Isonitrosocamphor (I) is converted to *aminocamphor* (II) by reduction; to *camphorquinone* (III) by the action of nitrous acid or sulphurous acid; and to two stereoisomeric *camphordioximes* (IV) by interaction with a molecular quantity of hydroxylamine. *Aminocamphor*, in presence of nitrous acid, yields *azocamphor* (V), which on heating passes into *azocamphanone* (VI) and nitrogen:



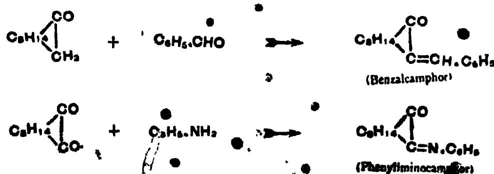
(ii) When camphor is treated with ethyl formate in presence of sodium, *oxymethylenecamphor* is produced, and this latter compound reacts with hydroxylamine to give *cyanocamphor* :



(iii) *Sodium camphor* (the sodium salt of enolic camphor), when heated to 288° in xylene (to protect it from atmospheric oxygen), yields *campholic acid*, $C_9H_{17}.COOH$ (p. 380), but, if carbon dioxide is present, *camphorcarboxylic acid* is formed at a much lower temperature :



(iv) Camphor can be condensed with aromatic aldehydes, and camphorquinone with amines, when *benzal-compounds* and *anils* result :



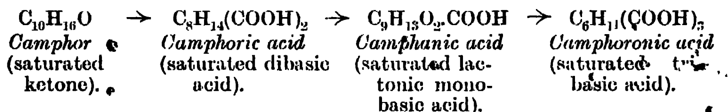
Compounds such as *benzalcamphor*, *phenyliminocamphor*, and *azocamphanone*, which contain a conjugated system of unsaturated groups adjacent to the carbonyl radicle, are distinguished by enormous optical activity, and also possess extraordinary refractive anomalies (*cf.* p. 349).

V. *Reduction*

By alkaline reduction, camphor yields a number of stereoisomeric secondary alcohols, the *borneols*. We shall return to these and their corresponding hydrocarbons later.

VI. *Oxidation*

When camphor is boiled with dilute nitric acid, the dibasic *camphoric acid* is produced; this may be oxidized further to *camphanic* and *camphoronic acids*:



$C_{10}H_{16}O$	→	$C_8H_{14}(COOH)_2$	→	$C_9H_{13}O_2.COOH$	→	$C_6H_{11}(COOH)_3$
Camphor (saturated ketone).		*Camphoric acid* (saturated dibasic acid).		*Camphanic acid* (saturated lactonic monobasic acid).		*Camphoronic acid* (saturated tribasic acid).

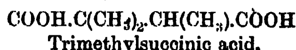
B. The Structure of some Acids related to Camphor

Before we can attack the problem of the ultimate constitution of camphor itself, we must elucidate those of some of the acids which have been encountered above. We shall consider in succession *camphoronic*, *camphoric*, *camphanic*, *apocamphoric*, and *campholic* acids.

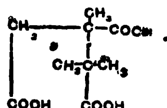
I. *Camphoronic Acid*, $C_6H_{11}(COOH)_3$

This tricarboxylic acid, which is the final oxidation product of camphor, camphoric acid, and camphanic acid, breaks down on destructive distillation into carbon dioxide, water, carbon, and a number of aliphatic acids, chief among which are *isobutyric* and *trimethylsuccinic* acids.



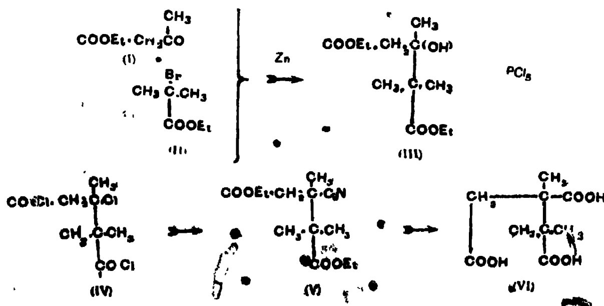


Evidently a group $> C(CH_3)$- has disappeared in the production of the former acid, and, similarly, a longer carbon chain has been destroyed in the case of trimethylsuccinic acid. It therefore seems probable that the three carboxyl groups in the above two acids represent the three individual acid radicles of camphoronic acid; but the total carbon content of the alkyl groups in the two acids is C_9, whereas that in camphoronic acid is only C_6. We have, therefore to fuse these two alkyl residues together, so to speak, so as to form a chain containing in all *six* carbon atoms. This can only be done in one way:



A synthesis of *camphoronic acid* by Perkin and Thorpe (1897) confirms this structure (which had previously been suggested by Bredt in 1893).

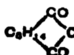
In presence of purified zinc dust, ethyl a-bromoisobutyrate (I) and ethyl acetoacetate (II) condense to β-oxy-aaβ-trimethylglutaric ester (III), which is converted by phorphorus pentachloride to the trichloride of the corresponding β-chloro-acid (IV). The ester of the latter acid reacts with alcoholic potassium cyanide, the chlorine radicle being replaced by the nitrile group -CN (V); saponification of this yields *aaβ-trimethyl-β-carboxyglutaric acid* (VI.; *aaβ-trimethylcarballylic acid*), which was found to be identical with *camphoronic acid*:



II. *Camphoric Acid*, $C_8H_{14}(COOH)_2$

The following points are important in finding the constitution of camphoric acid :

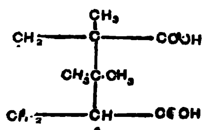
(i) It very readily (*e.g.* by simple distillation) forms camphoric anhydride,



(ii) It is oxidized to *camphoronic acid*, thereby losing one carbon atom entirely, whilst another is transformed to a carboxyl group.

(iii) By fusion with caustic potash, it yields *isopropylsuccinic* (and other) acids, $COOH.CH(C_3H_7).CH_2.COOH$.

The ready formation of an anhydride indicates that camphoric acid is a substituted succinic or glutaric acid, whilst the above structure of camphoronic acid proves almost beyond doubt that camphoric acid is derived from glutaric rather than from succinic acid. The only constitution which will harmonize this fact with the production of isopropylsuccinic acid on fusion of camphoric acid with potash is



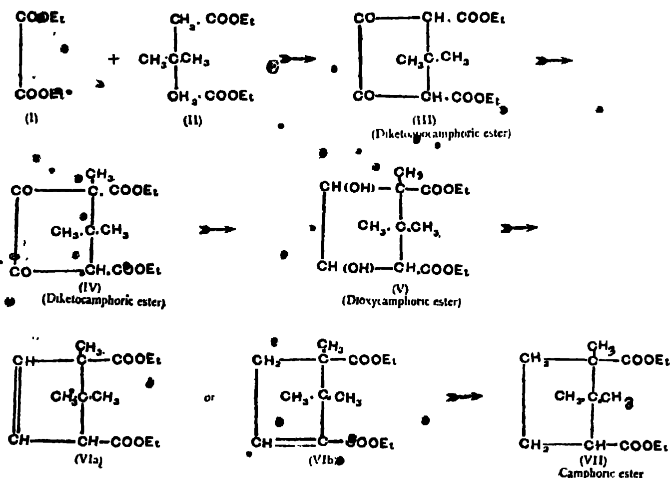
Camphoric acid was synthesized by Gustav Komppa in 1903; it may be mentioned that recently (1910) Blanc and Thorpe disputed the correctness of part of the experimental work involved in Komppa's synthesis. The criticism, however, appears to have been somewhat premature, for it was later entirely withdrawn.

The main features of the synthesis are as follows :—

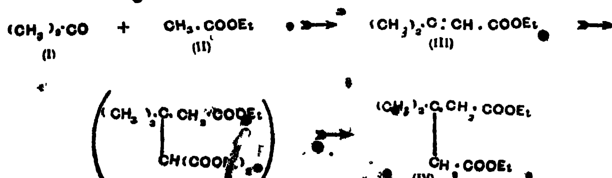
Oxalic ester (I) and *ββ-dimethylglutaric ester* (II, see below) are condensed by sodium ethylate to the ester of 1, 1-*dimethyl-3, 4-diketo-cyclopentane-2,5-dicarboxylic acid* (III). This compound forms a monosodium derivative, which by treatment with methyl iodide furnishes the *methylated* compound (IV); reduction of (IV) in presence of a very weak acid (CO_2) produces a *di-secondary alcohol* (V), which on prolonged treatment with phosphorus and boiling hydriodic acid furnishes the *ethylenic ester* (VIa

or VIb). Hydrogen bromide is united additively with the latter unsaturated hydrocarbon, and reduction of the resulting bromo-derivative with zinc dust and acetic acid yields *racemic diethyl camphorate* (VII).

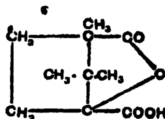
The *racemic camphoric acid* obtained from the ester is completely identical in properties with an equimolecular mixture of the *d*- and *l*-camphoric acids from natural *d*- and *l*-camphor, and the structure of camphoric acid is thus placed beyond doubt by Komppa's brilliant synthesis.



It may be mentioned that *ββ-dimethylglutaric ester* has been synthetically produced from acetone (I) and ethyl acetate (II). These condense in presence of sodium to *dimethylacrylic ester* (III), which by condensation with malonic ester and subsequent saponification and loss of CO_2 becomes the required substituted glutaric ester (IV):

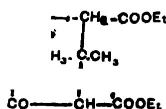


III. *Camphanic acid,* $C_9H_{13}O_2.COOH$, is a lactonic acid derived from camphoric acid by oxidation, and passing by further oxidation to camphoronic acid. In view of the constitutions of the two latter acids, that of camphanic acid must be

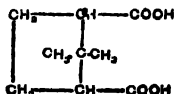


IV. *Apocamphoric Acid,* $C_7H_{12}(COOH)_2$.

We saw above that by condensation of oxalic ester with $\beta\beta$-dimethylglutaric ester there was formed an ester of the formula



If, instead of replacing one of the hydrogen atoms in this ester by the methyl radicle, the remaining stages of the camphoric acid synthesis are directly proceeded with, the next lower homologue of camphoric acid is finally obtained in place of the latter. The acid in question is known as *apocamphoric acid,* and must accordingly be formulated as



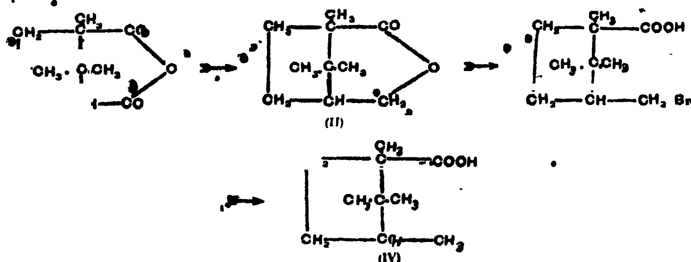
V. *Campholic acid,* $C_9H_{17}.COOH$.

We have already mentioned that when sodium is heated with camphor to 280° in an inert atmosphere, and the reaction product subsequently treated with water, *campholic acid,* possessing the composition $C_{10}H_{18}O_2$ (*i.e.* $C_{10}H_{16}O+H_2O$), is produced.

The structure of this acid is made clear by its synthesis from camphoric acid, which was accomplished in 1900 by Haller and Blanc.

Camphoric anhydride (I) can be reduced by sodium amalgam to *campholide* (II), in the same way that phthalic anhydride yields phthalide by reduction (*cf.* chap. iii. p. 31). The lactone *campholide* unites with

hydrogen bromide to produce a *bromo-acid* (III), which by reduction with zinc dust and acetic acid leads to *campholic acid* (IV):



C. The Constitution of Camphor (compare p. 373).

The following points, brought out in the preceding sections, are sufficient basis upon which to assign a structural formula to camphor itself :—

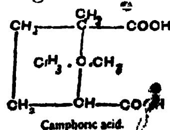
(i) It is oxidized to *camphoric acid*, $C_8H_{14}(COOH)_2$, in the course of which process no carbon atoms have been removed from the molecule.

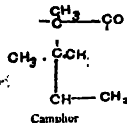
(ii) It is a ketone of the type $C_8H_{14}\left\langle\begin{array}{l}CO\\CH_2\end{array}\right.$.

(iii) It unites (to all intents and purposes) with a molecular proportion of water to form *campholic acid*.

(iv) It is easily transformed to *carvacrol* (p. 373).

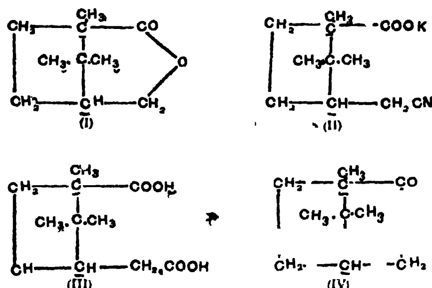
Arguing mainly from the probable constitution of *camphoric acid*, Bredt showed in 1893 that there must exist in camphor a dicyclic ring-system. Previous formulæ for camphor, such as those of Kekule (1873) and Kanonnikow (1883), had been conceived on a monocyclic basis. As indicated above, Bredt suggested the formula for camphoric acid which was confirmed ten years later by Komppa's synthesis, and he further put forward a corresponding structure for camphor :


Camphoric acid.


Camphor

This structural formula for camphor is supported, not only by reactions (ii) and (iii) cited above, but also by its synthesis from *camphoric acid* and *campholide* by Haller in 1896 :

Campholide unites additively with potassium cyanide and forms a *nitrile salt* (II), which is saponified to *homocamphoric acid* (III). *Calcium homocamphorate* yields *camphor* (IV) when distilled in a current of carbon dioxide :

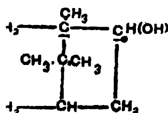


D. Reduction Products of Camphor.

I. *Alcohols*

When *camphor* is reduced in alkaline media, the corresponding secondary alcohol, *borneol*, is produced, together with a certain amount of an isomeric alcohol, *isoborneol.*

Borneol, which is therefore represented as



occurs in nature in both *d*- and *l*-varieties.

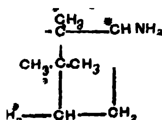
d-Borneol is found in the oils of spike, rosemary, and cardamom, and *l-Borneol* (which is the more abundant) in chamomile, tansy, citronella, valerian, sage, and thyme. Frequently these alcohols are present as esters, especially as *acetate* and *isovalerianate.*

Borneol resembles camphor to a certain extent in volatility and in smell, and is often termed "Borneo camphor." On oxidation it reverts to camphor in the first place, and then naturally gives camphoric acid and the other oxidation products of camphor itself.

The structure of *isoborneol* is not definitely proved at present, but it is evident that the isomerism is structural, and not simply geometrical.

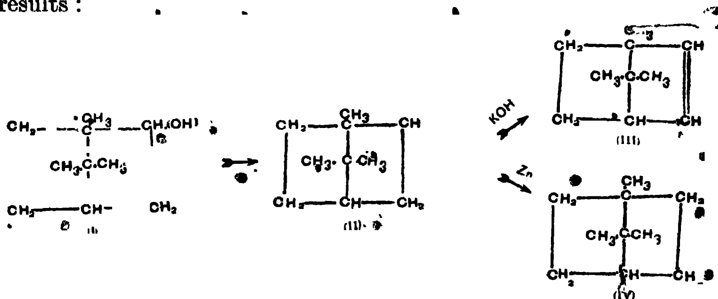
II. *Amines*

When *camphoroxime* is reduced (compare p. 374), a mixture of *bornylamine* (of the appended structure) and *neobornylamine* (which possibly corresponds to isoborneol) is produced.



III. *Hydrocarbons*

When *borneol* (I) is converted to *bornyl iodide* (II), and the latter treated with alcoholic potash, *bornylene* (III), $C_{10}H_{16}$, is slowly formed; on the other hand, if *bornyl iodide* (II) is carefully reduced with zinc dust, the saturated hydrocarbon *camphane*, $C_{10}H_{18}$ (IV), which is the parent substance of the camphor series, results:



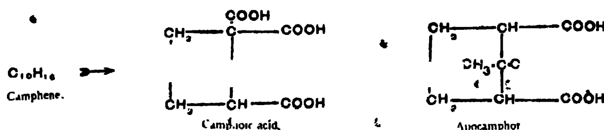
If, however, the corresponding *bornyl chloride* or *bornyl bromide* is boiled with alcoholic potash, bornylene is not formed, but an isomeric hydrocarbon, *camphene*, $C_{10}H_{16}$, which is found in nature in the oils of ginger, spike, valerian, and some turpentines, and is characterized by being the only solid unsaturated terpene hydrocarbon yet observed. It melts at 50°, and when heated with glacial acetic acid and a few drops of concentrated sulphuric acid, passes into *isobornyl acetate.*

Camphene is also produced :

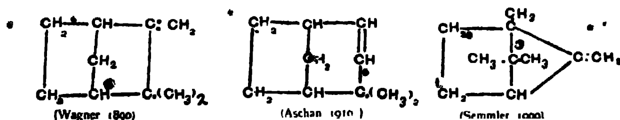
(i) When *isoborneol* is heated with dilute sulphuric acid ;

(ii) When *pinene hydrochloride* (p. 368) is warmed with sodium acetate and acetic acid.

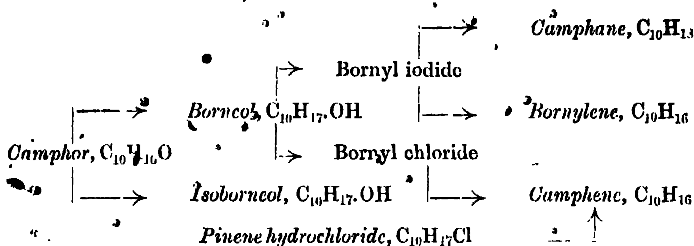
The constitution of *camphene* is not well understood ; when carefully oxidized it first produces *camphene glycol*, $C_{10}H_{16}(OH)_2$, and then (with nitric acid) *camphoic acid*, $C_7H_{11}(COOH)_3$. This acid loses a molecular proportion of carbon dioxide when heated above its melting-point (196°), and *apocamphoric acid* remains. This behaviour is represented by the following structural formulæ :



The following formulæ have been tentatively put forward at different times for *camphene*, but, as already stated, there is a lack of evidence which would permit of a definite decision of the question at present :



The relations of the two borneols to these different hydrocarbons are schematically represented below :



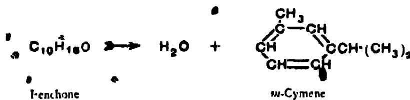
III. Derivatives of Fenchone

Fenchone is an isomeride of camphor which is present in oil of fennel (as *dextro*-variety) and as *lævo*-form (with thujone and pinene) in thuja oil.

Whilst, however, camphor and pinene belong to the *p*-menthane series, *fenchone* is related to the *meta*-series; at the same time, fenchone is a "saturated" compound in so far that it does not react additively with bromine or nitrosyl chloride, and hence it is doubtless a dicyclic or "bridged-ring" terpene.

The following reactions of *fenchone* are of interest from the light they shed upon its constitution.

(i) When it is distilled with phosphoric anhydride, *m*-cymene is produced:

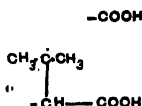


(ii) *Fenchone* does not form an oxymethylene derivative by condensation with formic ester in presence of sodium ethylate, nor an isonitroso-compound with amyl nitrite and sodium ethylate.

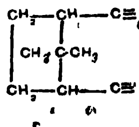
Hence it may be assumed that *fenchone does not contain the ketomethylene grouping* -CH_2.CO-.

(iii) *Fenchone* is remarkably stable with respect to oxidizing agents, but the intensive action of concentrated aqueous potassium

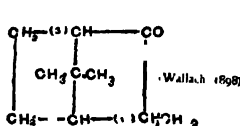
permanganate oxidizes it to a variety of acids, amongst which is found *apocamphoric acid:*

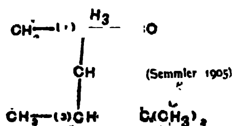


Fenchone is therefore related in some degree to camphor, in that it contains the residue

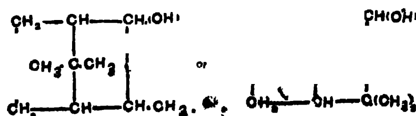


We have to correlate this fact with the above data that no $-CH_2.CO-$ group is present, and that the carbon atoms attached to the groups CH_3- and CH_3-C-CH_3 are in the 1,3- (or *meta*-) position to each other. This can be done in two ways, each of which has been put forward as a satisfactory representation of the chemical deportment of fenchone:

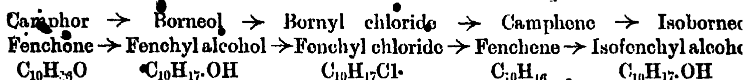




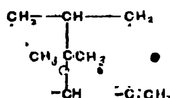
Fenchone is a liquid ketone, but resembles camphor somewhat in its smell. When attacked by alkaline reducing agents it yields *fenchyl alcohol* (of opposite rotatory power to the original ketone employed):



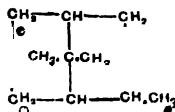
Fenchyl chloride results upon esterification of the alcohol with hydrogen chloride, and this ester, when warmed with aniline, yields a hydrocarbon *fenchene*, which by addition of water yields a new alcohol, *isofenchyl alcohol.* This is exactly analogous to the behaviour of the similar camphor compounds :—


Camphor → Borneol → Bornyl chloride → Camphene → Isoborneol
Fenchone → Fenchyl alcohol → Fenchyl chloride → Fenchene → Isofenchyl alcohol
$C_{10}H_{16}O$ $C_{10}H_{17}.OH$ $C_{10}H_{17}Cl$ $C_{10}H_{16}$ $C_{10}H_{17}.OH$

The behaviour of *fenchene* upon oxidation appears to indicate the presence of a group, $>C:CH_2$, and accordingly it has been formulated by Wallach as :



Hydrogenation of fenchene produces the saturated parent hydrocarbon of the fenchone series, *fenchane* :



IV. Relations between the Dicyclic Terpenes

We proceed to collect in tabular form the chief relations between the dicyclic terpene derivatives, including the compounds *carone* and *thujone*, dealt with in chapter xix. in connexion with the monocyclic ketone carvone.

Relations between the Dicyclic Terpenes

Ring-systems	*Hydrocarbons*	*Alcohols*	*Ketones*	*Acids*
Trimethylene hexamethylene (related to both *p*- and *m*-cymene)	$C_{10}H_{16}$ Thujene	$C_{10}H_{17}.OH$ Thujyl alcohol	$C_{10}H_{16}O$ *Carone* *Thujone*	Caronic acid, $C_6H_8(COOH)_2$
Tetramethylene hexamethylene (related to *p*-cymene)	$C_{10}H_{16}$ *Pinene*	$C_{10}H_{16}(OH)_2$ Pinol; Soberythritol, $C_{10}H_{16}(OH)_4$		Pinonic acid, $C_{10}H_{16}O_3$; Pinic acid, $C_9H_{16}O_4$
Pentamethylene hexamethylene (related to *p*-cymene)	*Camphene*, $C_{10}H_{16}$; Bornylene, $C_{10}H_{16}$; Camphane, $C_{10}H_{18}$	$C_{10}H_{17}.OH$ *Borneol*; Isoborneol	$C_{10}H_{16}O$ *Camphor*	Campholic acid, $C_{10}H_{18}O_2$; *Camphoric acid*, $C_{10}H_{16}O_4$; Apocamphoric acid, $C_9H_{14}O_4$
(related to *m*-cymene)	Fenchene, $C_{10}H_{16}$; Fenchane, $C_{10}H_{18}$	$C_{10}H_{17}.OH$ Fenchyl alcohol; Isofenchyl "	$C_{10}H_{16}O$ *Fenchone*	

V. The Sesquiterpenes

There are a number of hydrocarbons of the composition $C_{15}H_{24}$ found in certain essential oils, and known as sequiterpenes. Very little is yet known as to their constitution, and although Wallach, Harries, and other well-known investigators in this branch are now devoting attention to this problem, sufficiently definite results have not been announced up to the present for this class of compounds to be described here in any detail.

We may mention, however, that whilst the *hemiterpene* isoprene, C_5H_8, boils at 37°, and the majority of the true *terpenes*, $C_{10}H_{16}$, at 170-180°, the *sesquiterpenes* are thick oils of much higher boiling-point (260-280°). Most of the latter seem to

contain two ethylenic linkings, and are therefore probably of a dicyclic nature. The chief members of the group are :

Cadinene, widely distributed in oils of cade, German and Swedish pines, cedarwood, cubebs, wormwood, and betelnut.

Caryophyllene, found in oil of cloves.

Humulene, from oil of hops.

Patchoulene, from Patchouli camphor.

A few *diterpenes* ($C_{20}H_{32}$) have also been from time to time reported to exist in nature, but at present little definite knowledge exists concerning them.

APPENDIX TO CHAPTERS XVIII–XXI

TABLES SHOWING THE CHIEF RELATIONSHIPS BETWEEN THE MONOCYCLIC, DICYCLIC, AND OLEFINIC TERPENES, AND THE AROMATIC SERIES

I. Aromatic Compounds and Terpenes

(a) *THE para-SERIES*

Type	*Aromatic series*	*Terpenes* — *Monocyclic*	*Terpenes* — *Dicyclic*	*Terpenes* — *Olefinic*
Hydrocarbons	*p-Cymene*, $C_{10}H_{14}$	*Dipentene*, $C_{10}H_{16}$ Menthene, $C_{10}H_{18}$	*Pinene*, $C_{10}H_{16}$	(*Isoprene*, C_5H_8)
Alcohols (Phenols)	*p* Cresol, $C_6H_4(CH_3)OH$ *Carvacrol*, $C_{10}H_{13}.OH$ Thymol, $C_{10}H_{13}.OH$	*Terpineol*, $C_{10}H_{17}.OH$		
Aldehydes				*Citral*, $C_{10}H_{16}O$
Ketones		*Carvone*, $C_{10}H_{14}O$ Menthone, $C_{10}H_{18}O$	*Camphor*, $C_{10}H_{16}O$ Thujone, $C_{10}H_{14}O$	
Acids	*p*-Oxybenzoic acid, $C_6H_4(OH).COOH$			
Base	β-Methylpyrrolidine			

(b) *THE meta-SERIES*

Type	*Aromatic series*	*Monocyclic terpenes*	*Dicyclic terpenes*
Hydrocarbons	*m Cymene*, $C_{10}H_{14}$	Sylvestrene, $C_{10}H_{16}$ Carvestrene, $C_{10}H_{16}$	
Ketones			*Fenchone*, $C_{10}H_{16}O$
Acids	*m* Oxybenzoic acid, $C_6H_4(OH).COOH$		

II. MONOCYCLIC AND DICYCLIC TERPENES

Type	*Monocyclic*	*Dicyclic* (*Trimethylenic*)	(*Tetramethylenic*)	(*Pentamethylenic*)
Hydrocarbons	(*p*) *Dipentene*, $C_{10}H_{16}$ (*p*) Terpinene, $C_{10}H_{16}$ (*m*) Carvestrene, $C_{10}H_{16}$		*Pinene*, $C_{10}H_{16}$	Camphene, $C_{10}H_{16}$
Alcohols	(*p*) *Terpineol*, $C_{10}H_{17}.OH$ (*p*) Terpin hydrate, $C_{10}H_{18}(OH)_2H_2O$			Isoborneol, $C_{10}H_{17}OH$
Ketones	(*p*) *Carvone*, $C_{10}H_{14}O$	(*p*) Carone, $C_{10}H_{14}O$		*Camphor*, $C_{10}H_{16}O$

III. MONOCYCLIC AND OLEFINIC TERPENES

Type	*Monocyclic*	*Olefinic*	(*Related to olefinic*)
Hydrocarbons	*Dipentene*, $C_{10}H_{16}$ Terpinene, $C_{10}H_{16}$ (Dihydro-*m*-xylene, $(CH_3)_2C_6H_6$)	(*Isoprene*, C_5H_8)	
Alcohols, etc.	*Terpin hydrate*, $C_{10}H_{18}(OH)_2H_2O$ Cineol, $C_{10}H_{18}O$	*Geraniol*, $C_{10}H_{17}.OH$ *Nerol*, $C_{10}H_{17}OH$ Linalool, $C_{10}H_{17}.OH$	
Aldehydes		Citronellal, $C_{10}H_{18}O$	
Ketones	Pulegone, $C_{10}H_{16}O$	*Citral*, $C_{10}H_{16}O$	*Methylheptenone*, $C_8H_{14}O$

INDEX OF SUBSTANCES

(References in Roman type indicate general or passing mention of a compound; those in *italics* give the pages where particular characteristics of the substance will be found.)

GENERAL AND AUTHOR INDEX

(Names of authors are in *italics*)

PRINTED BY
TURNBULL AND SPEARS,
EDINBURGH